Intervention

A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial

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KEYWORDS
Stent, eluting stent, everolimus, randomised trial

Abstract

Background: *Everolimus has been successfully tested in humans using both an erodable and a durable polymer in small previous studies.*

Methods: *This single blind multi-centre non-inferiority randomised (3:1) controlled trial evaluated the safety and performance of the XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) versus the TAXUS Paclitaxel Eluting Coronary Stent System (TAXUS® PECSS) in the treatment of patients with a maximum of two de novo native coronary artery lesions located in two different epicardial vessels. Three hundred patients with evidence of myocardial ischaemia were allocated to stent implantation with an everolimus-eluting stent (n=223) or a paclitaxel-eluting stent (n=77). Suitable lesions had a diameter stenosis of ≤50-99%, a length of ≤28 mm, and a reference vessel diameter between 2.5 mm and 4.25 mm. The primary endpoint was in-stent late loss (LL) at 180 days. Percentage in-stent volume obstruction (%VO) was measured by intravascular ultrasound (IVUS) in a subset of 152 patients. Clinical secondary endpoints included ischaemia driven major adverse cardiac events (ID-MACE) at 180 days.*

Results: *At 6 months, the in-stent LL was 0.11±0.27 mm in the everolimus-eluting stent arm, as compared to 0.36±0.39 mm in the paclitaxel-eluting stent arm (p<0.0001). Percentage VO in the everolimus-eluting stent arm was 2.5±4.7% versus 7.4±7.0% in the paclitaxel-eluting stent arm (p<0.0001). Hierarchical MACE was 2.7% (6/222) in the everolimus-eluting stent arm vs. 6.5% (5/77) in the paclitaxel-eluting stent arm.*

Conclusion: *This non-inferiority randomised trial not only met its primary endpoint, but also demonstrated the superiority of the everolimus-eluting stent over the paclitaxel-eluting stent in terms of in-stent late loss.*

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Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia and reduce restenosis and associated clinical events.[1,2]

Everolimus is an effective anti-proliferative agent that inhibits growth factor-stimulated cell proliferation by causing cell cycle arrest in the late G1 stage in the cell cycle.[3]

The feasibility of using everolimus on a drug-eluting stent was demonstrated in the earlier FUTURE I[4,5] and FUTURE II[6,7] studies and more recently in the SPIRIT FIRST[8] study, using the everolimus-eluting stent. The SPIRIT FIRST study (N=60) was a multi-centre, single blinded controlled study conducted to assess the feasibility and efficacy of the everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions compared to the metallic, uncoated MULTI-LINK VISION RX Coronary Stent. This feasibility trial showed clinical safety and the angiographic in-stent Late Loss (LL) observed was 0.10 mm, a reduction of 88% relative to the bare metal stent at six months and an in-stent LL of 0.24 mm at 12 months, which was a reduction of 71%.[8,9]

The SPIRIT II trial is a continuation of the assessment of the safety and performance of the XIENCE V everolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in the treatment of patients with a maximum of two de novo native coronary artery lesions.

Methods

Patient selection

This prospective, randomised (3:1) single-blind, parallel two-arm trial was performed at 28 centres in Europe, India and New Zealand and enrolled patients from July 2005 to November 2005. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were older than 18 years and had evidence of myocardial ischaemia. The patient could have a maximum of two de novo native coronary artery lesions, which had to be located in different major epicardial vessels. The de novo target lesion(s) had to have a reference vessel diameter between 2.5 mm and 4.25 mm by visual estimation, a target lesion length ≤28 mm, a visually estimated stenosis between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrolment if they had known diagnosis of acute myocardial infarction three days prior to the baseline procedure, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, paclitaxel, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated. Additionally, patients having target lesion(s) with an aorto-ostial or left main location, a lesion located within 2 mm of the origin of the left anterior descending- or left circumflex, heavy calcification, or a visible thrombus within the target vessel were also excluded from the trial.

The everolimus-eluting stent

The XIENCE V Everolimus Eluting Coronary Stent System (EECSS) (Advanced Cardiovascular Systems, an Abbott Vascular Company, IL, USA) is comprised of the ACS MULTI-LINK VISION Stent and delivery system, and a drug eluting coating. The ACS MULTI-LINK VISION Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a non-erodable polymer, coated over another non-erodable polymer primer layer. The coating comprises acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimetre of stent surface area with no topcoat polymer layer. The stent is designed to release approximately 80% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation.[10] Everolimus has received market approval in the European Union and the XIENCE V EECSS has received CE mark in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria prior to the procedure, patients were enrolled through a telephone randomisation service and assigned in a 3:1 ratio to either an everolimus-eluting stent or a paclitaxel-eluting stent. The stents were available in lengths of 8, 18 and 28 mm, and diameters of 2.5, 3.0, 3.5 and 4.0 mm. Lesion lengths greater than 22 or less than or equal to 28 mm were to be covered by 2 stents; twice an 18 mm stent, or a 28 mm and an 8 mm stent.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the burst pressure rate. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was left to the discretion of the physician, however, if performed, it was only to be done with balloons sized to fit within the boundaries of the stent. In the event of a bailout procedure and additional stent requirement, the stent had to be one from the same arm as the first implanted stent. IVUS was performed in a subset of 152 consecutive patients enrolled in pre-selected centres, after angiographically optimal stent placement had been obtained, and was repeated if additional post-dilatation was performed to optimise stent apposition and/or deployment.

Peri-procedural pharmaceutical treatment was administrated according to standard hospital practice. Either unfractionated heparin or bivalirudin could be used for procedural anticoagulation. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the physician. All patients enrolled into the study were pre-treated with a loading dose of 300 mg of clopidogrel and maintained on 75 mg of clopidogrel daily for a minimum of 6 months and ≥75 mg of aspirin daily for a minimum of one year following the procedure. Clinical device success was defined as a successful delivery and

deployment of the first inserted study stent (in overlapping stent setting a successful delivery and deployment of the first and second study stent) at the intended target lesion with attainment of final residual stenosis of 50% of the target lesion by QCA (by visual estimation if QCA unavailable). Bailout patients were included as clinical device success only if the above criteria for clinical device success were met.

Clinical procedure success included the previous criteria of clinical device success, but with the addition of any study stent or other stent devices and required the absence of ID-MACE during the hospital stay. In dual lesion setting both lesions had to meet clinical procedure success.

Follow-up

Patients were evaluated at 30 and 180 days. Further evaluations will be performed at 270 days, 1 and 2 year(s) and will form the subject of additional reports. At outpatient visits, patients were asked specific questions about the interim development of angina or the occurrence of MACE. Angiographic follow-up for all patients and IVUS in a subset of 152 consecutive patients (enrolled at selected centres) were performed at 180 days, and both investigations will be repeated at 2 years for this subset of patients. Prior to performing a follow-up angiogram, the physician was required to record prospectively in the eCRF whether a revascularisation (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands).[11] In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analysed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference vessel diameter (RVD) obtained by an interpolated method, and percentage diameter stenosis (%DS). Binary restenosis (BR) was defined in every segment as diameter stenosis ≥50% at follow-up. Late loss (LL) was defined as the difference between MLD post-procedure and MLD at follow-up.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array intravascular ultrasound (Eagle-eye™ Volcano, Atlantis™, Boston Scientific) using automated pull-back at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm.[12] The stent volume (SV) and lumen volume (LV) were calculated according to the Simpson's rule.[13] The intrastent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intrastent neointimal volume/stent volume*100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*.[13] Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late-acquired incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.[14-16]

Study endpoints

The primary endpoint was angiographic in-stent LL, as determined by quantitative angiography, based on an "analysis lesion": one randomly selected lesion per patient to avoid inter-lesion dependence[20]. Secondary endpoints (QCA and IVUS) at 180 days and 2 years (subset of 152 consecutive patients enrolled at selected centres) included the in-stent, in-segment, proximal and distal LL; in-stent and in-segment angiographic binary restenosis rate and %DS; in-stent percentage volume obstruction (%VO) and plaque behind the stent; and persisting and late-acquired incomplete stent apposition, aneurysm, thrombosis and persisting dissection. In-stent was defined as within the margins of the stent while in-segment was defined as located within the margins of the stent and 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the post-procedure and follow-up minimum luminal diameters.

Secondary clinical endpoints included Ischaemia-Driven MACE (comprised of cardiac death, myocardial infarction and Ischaemia-Driven Target Lesion Revascularisation [ID-TLR]) either by CABG or PCI, evaluated at 30, 180 and 270 days, 1 and 2 year(s) after the index procedure and acute success including clinical device and clinical procedure success.

All deaths that could not be clearly attributed to another cause were considered cardiac deaths.

A non-Q-wave myocardial infarction was defined as a typical rise and fall of CK-MB* with at least one of the following: ischaemic symptoms, ECG changes indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention. (*if non-procedural/spontaneous MI, CK-MB ≥2 times upper limit of normal; if post PCI, CK-MB ≥3 times upper limit of normal; if post CABG, CK-MB ≥5 times upper limit of normal).

ID-TLR was defined as a revascularisation at the target lesion associated with any of the following: non-invasive positive functional ischaemia study (e.g. exercise testing or equivalent tests) or invasive positive functional ischaemia study (e.g. Fractional Flow Reserve [FFR] or Coronary Flow Reserve [CFR]); ischaemic symptoms and an angiographic%DS ≥50% by on-line quantitative coronary angiography (QCA);%DS ≥70% by on-line QCA without either ischaemic symptoms or a positive functional study. The investigator assessment could potentially be overruled by QCA off-line from the core laboratory.

Stent thrombosis, categorised as acute (≤1 day), subacute (> 1 day ≤30 days) and late (> 30 days), was defined as any of the following: in the presence of angiography, clinical presentation of acute coronary syndrome[17] with angiographic evidence of stent thrombosis. In the absence of angiography: cardiac death or acute MI in the territory of the stented vessel/vessels; AMI that could not be distinctly attributed to a non-target vessel during the Clinical Events Committee adju-

dication was considered in the composite for stent thrombosis. The endpoints were adjudicated by an independent clinical events committee (appendix I). In addition, a data and safety monitoring board that was not affiliated with the study reviewed the data to identify any safety issues related to the conduct of the trial (appendix I).

Statistical analysis

The primary endpoint and all trial endpoints were analysed on both the intent-to-treat and per-treatment evaluable populations, the latter of which consisted of patients who had no major protocol deviations, as evaluated in a blinded manner.

The sample size for the study was determined based on the primary endpoint of in-stent LL at 180 days and on the following assumptions: one-tailed non-inferiority test, overall α equals 0.05, randomisation ratio was 3 (everolimus arm):1 (paclitaxel arm), the true mean in-stent late loss was assumed to be 0.32 mm in the XIENCE V arm and 0.39 mm in the TAXUS arm, a non-inferiority margin delta (δ) of 0.16 mm and the group sequential design was based on the method described in Reboussin, et al. indexed by O'Brien & Fleming boundary.[18,19] Four interim analyses were planned and the final analysis was performed at the 0.0448 adjusted significance level. Given the above assumptions, analysing 180 patients in the test arm and 60 patients in the active control arm provides more than 91% power. In order to account for drop-outs and to ensure enough angiographic data, approximately 300 patients had to be enrolled of which 225 in the everolimus arm and 75 in the paclitaxel arm.

In this paper binary variables were compared using the Fisher's exact test. Continuous variables were compared using Wilcoxon two-sample test. The hypothesis testing for the primary endpoint was performed using a one-sided non-inferiority test with asymptotic test statistic. If non-inferiority would be shown, superiority analysis was planned using a two-sided t-test at the 5% alpha level. Due to inclusion of dual vessel/lesion treatment, as a secondary analysis, a repeated measures analysis using all target lesions was performed and compared with the analysis using 'analysis lesion'. Final 6-month results are presented in this manuscript.

Results

Patient characteristics

Between July 2005 and November 2005, 223 patients were randomly assigned to receive the everolimus eluting stent, and 77 were assigned to receive the paclitaxel eluting stent. As defined in the protocol, all results are presented for the intent-to-treat population; 222 patients in the everolimus arm, and 77 patients in the paclitaxel arm (Figure 1). In the everolimus arm there was one withdrawal prior to 180 days. The two arms were similar with respect to baseline clinical variables examined in Table 1.

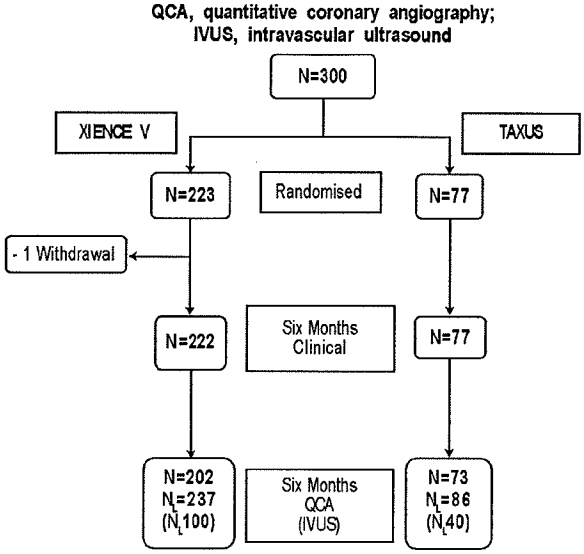
Procedural characteristics

The lesions in the two arms were treated similarly with the use of conventional techniques. Per patient, 1.4 study stents were implanted in the everolimus arm and 1.3 in the paclitaxel arm. Mean stent

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment arm.*

	Everolimus stent (n=223)	Paclitaxel stent (n=77)	All patients (n=300)
Age(yrs)	62±10	62±9	62±10
Male gender (%)	71	79	73
Current Smokers (%)	32	30	31
Diabetes (%)	23	24	23
Hypertension Requiring Medication (%)	67	65	67
Hyperlipidaemia Requiring Medication (%)	69	75	70
Prior TV Intervention (%)	4	4	4
Prior MI (%)	35	25	32
Stable Angina (%)	62	62	62
Unstable Angina (%)	27	32	28
Target Vessel (%)	N_L=260**	N_L=91**	N_L=351**
Left Anterior Descending	41	47	42
Left Circumflex	29	19	26
Right Coronary Artery	30	34	31
AHA / ACC#			
Lesion Class (%)			
A	1	0	1
B1	21	20	21
B2	65	67	66
C	13	13	13
Reference Vessel Diameter (mm±SD)***	2.70±0.52	2.82±0.58	2.73±0.54
Lesion Length (mm±SD)	13.0±5.7	13.2±6.4	13.0±5.9

* There were no significant differences between the treatment arms; ** N_L = lesion number; *** RVD pre p=0.099; difference: –0.12 [–0.26;0.02]
# AHA/ACC = American Heart Association/American College of Cardiology



One patient crossed over from the XIENCE V to TAXUS arm but is still counted in the XIENCE V arm (Intent to Treat)

Figure 1. Flowchart of patients.

deployment pressure was 15 atmospheres in each arm and post dilatation was performed in 39% of lesions in the everolimus arm and 27% of lesions in the paclitaxel arm. Bail out study stents were used in 5.4% of lesions in the everolimus arm and 4.5% of lesions in the paclitaxel arm. Both arms had similar rates of clinical device success 98.8% (256/259) for the everolimus arm vs. 98.9% (89/90) for the paclitaxel arm and they did not differ significantly with respect to the rate of clinical procedure success 99.1% (221/223) in the everolimus arm and 97.4% (75/77) in the paclitaxel arm.

Quantitative coronary angiography analysis

Angiographic data at 180 days was available for 275 analysable patients (92%). Pre-procedure, the RVD of the everolimus arm tended to be smaller than in the paclitaxel arm without reaching statistical significance. Post-procedure, this difference became significant at 5% alpha. The significantly smaller MLD pre-procedure and a slightly smaller acute gain in the everolimus arm resulted in a statistically significant difference in post-procedure MLD (2.49mm vs. 2.62 mm; –0.13 [–0.24;–0.03]) (Table 2). At 180 days, the mean in-stent LL (analysis lesion, intent-to-treat population) was significantly lower for the everolimus arm compared to the paclitaxel arm, 0.11±0.27mm versus 0.36±0.39mm (non-inferiority p<0.0001, superiority p<0.0001). (Figure 2)

For the per lesion analysis, the mean in-stent MLD,%DS and BR rate were 2.38±0.50 mm, 16±10% and 1.3% (3/237), respectively in the everolimus-eluting arm, as compared to 2.27±0.54 mm, 21±12%, and 3.5% (3/86) in the control arm. Figure 2 shows the cumulative distribution frequency curve of diameter stenosis at 180 days in each treatment arm. Table 2 shows the results of sub-segmental quantitative angiographic analysis for both treatment arms. The in-segment, proximal, and distal LL were non-statistically different between the two arms. However, the in-segment %DS was significantly lower in the everolimus arm.

Table 2. Results of sub-segmental quantitative coronary angiographic analysis

	Proximal Edge			In Stent			Distal Edge			In Segment Analysis		
	Everolimus stent (N_L=237)	Paclitaxel stent (N_L=86)	P-value	Everolimus stent (N_L=237)	Paclitaxel stent (N_L=86)	P-value	Everolimus stent (N_L=237)	Paclitaxel stent (N_L=86)	P-value	Everolimus stent (N_L=237)	Paclitaxel stent (N_L=86)	P-value
Reference vessel diameter (mm)												
Pre-procedure	na	na		2.70±0.52	2.82±0.58	0.099	na	na		na	na	
Post- procedure	na	na		2.86±0.43	3.00±0.48	0.019	na	na		2.78±0.47	2.89±0.49	0.049
At 6 months	na	na		2.81±0.47	2.87±0.51	0.315	na	na		2.75±0.49	2.85±0.53	0.061
MLD/LL (mm)												
MLD pre-procedure	na	na		1.06±0.42	1.14±0.36	0.032	na	na		na	na	
Acute Gain	na	na		1.43±0.43	1.48±0.38	0.232	na	na		na	na	
MLD Post- procedure	2.60±0.53	2.73±0.68	0.155	2.49±0.40	2.62±0.45	0.031	2.26±0.50	2.31±0.57	0.550	2.15±0.44	2.22±0.53	0.269
LL at 6 months*	na	na		0.11±0.27	0.36±0.39	<0.0001**	na	na		na	na	
LL at 6 months***	0.12±0.39	0.16±0.40	0.699	0.12±0.29	0.37±0.38	<0.0001	0.02±0.35	-0.01±0.37	0.650	0.07±0.33	0.15±0.38	0.084
MLD at 6 months	2.50±0.60	2.59±0.65	0.328	2.38±0.50	2.27±0.54	0.153	2.26±0.59	2.33±0.58	0.354	2.10±0.51	2.08±0.54	0.838
Diameter Stenosis (%)****												
Pre-procedure	na	na		61±12	59±10	0.173	na	na		na	na	
Post-procedure	10±6	10±7	0.710	13±6	13±6	0.486	12±5	12±6	0.164	23±9	23±11	0.779
At 6 months	11±9	10±7	0.694	16±10	21±12	<0.0001	12±8	12±7	0.398	24±12	27±13	0.013
Binary Restenosis (%)****												
At 6 months	0.4	0.0	1.000	1.3	3.5	0.194	0.4	0.0	1.000	3.4	5.8	0.343

* Analysis lesion intent to treat (primary endpoint in-stent late loss); ** P value for both non-inferiority (delta 0.16mm) and superiority; *** Per lesion analysis;
**** In-stent and in-segment based on interpolated RVD; proximal and distal based on mean edge diameter; MLD: Minimal Luminal Diameter; LL: Late Loss; N_L: lesion number at follow-up.

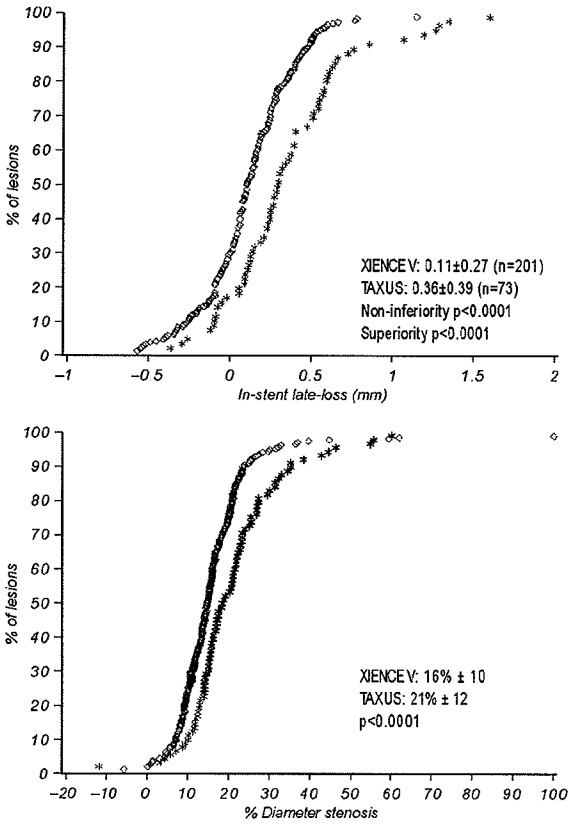


Figure 2. Cumulative frequency of in-stent late loss (analysis lesion) and in-stent percentage diameter stenosis at follow-up (all lesions).

Intravascular ultrasound evaluation

At 180-days, intravascular ultrasound evaluation showed no significant differences between the two arms with respect to the volume of the stent or the lumen volume (Table 3). However, there was a significant difference in vessel volume which reflects the small imbalance in vessel size seen at baseline between the everolimus and paclitaxel arms and the nominal stent volume (calculation based on the nominal stent diameter and stent length) which was 186 mm³ in the paclitaxel arm and 173 mm³ in the everolimus arm. Significantly less neointimal hyperplasia was observed in the everolimus-eluting stent arm compared to the paclitaxel-eluting stent arm (4±7 mm³ vs. 14±16 mm³, p<0.001) and similarly, significantly less %VO, (2.5±4.7% vs. 7.4±7.0%, p<0.001). Figure 3 shows the cumulative frequency distribution curve of %VO.

Of the seven patients in the everolimus arm in which post-procedure stent malapposition was observed, three were persisting, three were resolved and one was not evaluable at 180 days. In the paclitaxel arm both cases of stent malapposition observed post-procedure were resolved at 180 days. There were no cases of late acquired stent malapposition in either arms.

Table 3. IVUS Measurements at 6 months follow-up

	Everolimus stent (N_L=100)	Paclitaxel stent (N_L=40)	P-value
Vessel volume (mm³)	340±160	408±208	0.030
Stent volume (mm³)	167±85	192±97	0.157
In-stent neo-intima volume (mm³)	4±7	14±16	<0.001
Lumen volume (mm³)	164±85	178±92	0.409
In-stent volume obstruction (%) ‡	2.5±4.7	7.4±7.0	<0.001

‡ In-stent volume obstruction=100*(In-stent neo-intima volume/Stent volume)

Major adverse cardiac events

Major adverse cardiac events (MACE) are listed in Table 4. Hierarchically, for the intent-to-treat population in the everolimus

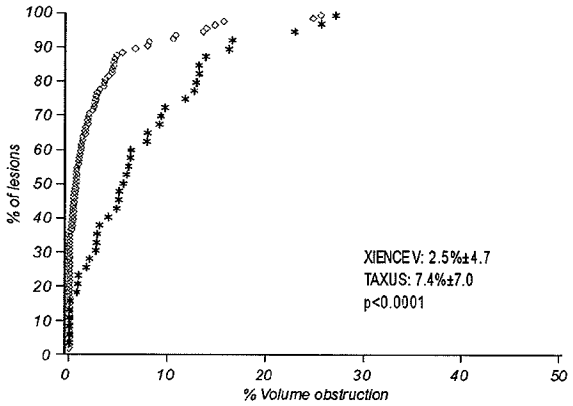


Figure 3. Cumulative curve of in-stent percentage volume obstrtion.

Table 4. Major adverse cardiac events and stent thrombosis events at 6 months in intent to treat population

	Everolimus stent n=222	%	Paclitaxel stent n=77	%
Hierarchical events				
Cardiac death	0	0	1	1.3
Myocardial infarction				
Q-wave	0	0	0	0
Non-Q-wave	2	0.9	2	2.6
Re-intervention				
ID-TLR-CABG	0	0	0	0
ID-TLR-PCI	4	1.8	2	2.6
Major adverse cardiac events	6	2.7	5	6.5
Non-hierarchical revascularisations				
ID-TLR	4	1.8	3	3.9
Non-ID-TLR	2	0.9	2	2.6
All TLR	6	2.7	5	6.5
Stent thrombosis	N	%	N	%
Acute	0	0	0	0
Sub-acute	0	0	0	0
Late	1*	0.5	1#	1.3

*Everolimus patient: at 53 days, dual antiplatelet therapy ongoing
#Paclitaxel patient: at 56 days, fainting, asystole, resuscitation and death, dual antiplatelet therapy ongoing
ID=Ischaemia Driven

arm two (0.9%) non-fatal non-Q wave MIs and four (1.8%) ID-TLRs by PCI were identified compared to one cardiac death (1.3%), two (2.6%) non-fatal non-Q wave MIs and two (2.6%) ID-TLRs by PCI in the paclitaxel arm. The total hierarchical MACE rate was 2.7% (6/222) in the everolimus-eluting arm vs. 6.5% (5/77) in the paclitaxel-eluting arm. In addition there were two (0.9%) ID-TVRs (non-target lesions) in the everolimus arm and none in the paclitaxel arm. There were 0.9% (2/222) and 2.6% (2/77) non-ID TLRs in the two arms respectively.

There were no occurrences of acute or sub-acute stent thromboses in either arm. One case of late stent thrombosis occurred in the everolimus arm at 53 days following a complex procedure with multiple stent implants. One case of late stent thrombosis occurred also in the paclitaxel arm at 56 days post procedure. The latter patient presented with a myocardial infarction and subsequently died. Both patients were taking dual antiplatelet therapy at the time of their thrombotic event.

Discussion

The Spirit II trial has met its primary endpoint, namely it shows an in-stent late loss in the everolimus arm, which is not only non-inferior but also superior to the in-stent late loss observed in the paclitaxel arm.

At the time of the design of the trial, it was decided – in order to avoid potential inter-lesion dependence[20] – to analyse only one lesion per patient (selected by a randomised process) for the primary endpoint, when the patient had received a stent in two different target vessel lesions (17% in the XIENCE V arm and 18% in the TAXUS arm). When all lesions were included in the analysis, the in-stent late loss remained unchanged (0.11 mm vs. 0.12 mm in the XIENCE V arm and 0.36 mm vs. 0.37 mm in the TAXUS arm). (Table 2).

Although a 3:1 randomisation everolimus vs. paclitaxel was performed, which provided more precision for the everolimus arm, without loss of power for the comparison; this might have resulted in a small imbalance in baseline characteristics pre- and post-procedure.

A trend towards a smaller pre-procedural vessel size in the everolimus arm was observed and this difference became significant post-procedure. These differences in vessel size and MLD post-procedure between the two arms could have impacted the restenosis rate and late loss as frequently demonstrated in the literature.[21-23] The MLD post-procedure in the everolimus arm is significantly smaller than the MLD post-procedure in the paclitaxel arm; this is the result of a smaller pre-treatment MLD (p-value 0.032) combined with a smaller acute gain (ns), although the deployment was done at equal levels of pressure. Despite this potential handicap at baseline, in-stent LL and%DS at follow up were significantly lower in the everolimus arm. This small difference in vessel size at baseline is also exemplified in stent volumes measured at baseline (162 mm^3 vs. 195 mm^3) and at follow-up (167 mm^3 vs. 192 mm^3) between the everolimus and paclitaxel arms respectively. Although this difference in stent volume does not achieve significance, it could have also impacted the late proliferative process as previously reported in the literature.[24] Nevertheless, we found a profound and highly significant reduction (73% reduction) in neointimal volume in the everolimus arm (3.8 mm^3) when compared to the paclitaxel arm (14.4 mm^3). Of interest was that in the IVUS findings of the SIRIUS study, assessing the efficacy of a DES coated with a comparable limus, an almost equal neointimal volume of 4.1 mm^3 was found.

Whether malapposition can be held responsible for late stent thrombosis in patients who receive drug-eluting stent remains so far unknown.[25,26] In the present population both drug-eluting stents show negative values of late loss, but the frequency of observations of negative late loss values within the everolimus arm is higher than in the paclitaxel arm (71/237=30% vs. 14/86=16%). The largest negative value was observed in the everolimus arm (–0.57 mm compared to –0.37 mm) in the paclitaxel arm. However, we must recognise that late loss is a parameter with a rather large standard deviation when inter-observer variability is assessed (1 SD 0.36 mm, 2 SD 0.72)[11]; and that late loss is the result of two individual measurements (MLD post-procedure, and MLD at follow-up) which both have their own inter-observer variability due mainly to the process of calibration.[27] Therefore, a negative late loss of –0.57 mm is still within the limits of the confidence level for the reproducibility of the late loss parameter. To investigate the relationship between late loss and malapposition, we have examined the lesions (n=23) with negative late loss, which were assessed by IVUS at follow-up and which received an everolimus-eluting stent and which could therefore potentially have a late-acquired or persisting stent malapposition. Among the 23 lesions with a negative late loss, there was not a single case of late-acquired malapposition, and only one case of persisting malapposition.

In the present study, the incidence of diabetics in the everolimus- and paclitaxel arms was 23% (51/223) and 24% (18/76) respectively. The in-stent LL in the paclitaxel arm for the diabetic patients was 0.39 mm, which is comparable to the previously reported late loss of 0.43 mm in a meta-analysis of the diabetic subsets of the TAXUS family trials.[28] In contrast, the LL in the diabetic patients in the everolimus arm was only 0.15 mm (SD 0.26) and thereby significantly superior to the loss of the paclitaxel arm which was 0.39 mm (SD 0.34). The difference in in-stent LL between everolimus- and paclitaxel-eluting stent was 0.24 mm (95% confidence interval: –0.41 mm; –0.08 mm). It is noteworthy that this difference is identical to the difference in late loss observed in the whole population, and thus indicates also superiority of everolimus-eluting stent versus the paclitaxel eluting stent in terms of LL reduction in the diabetic subset. However as this was not a pre-planned analysis further studies will be required to confirm this.

Conclusions

This non-inferiority randomised trial not only met its primary endpoint, but also demonstrated the superiority of the everolimus-eluting XIENCE V stent over the TAXUS paclitaxel-eluting stent in terms of in-stent late loss. In addition, the IVUS results showed that the XIENCE V stent was more effective at reducing neointimal hyperplasia than the TAXUS stent. The incidence of major adverse events was low and comparable between both treatment arms.

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Appendix I

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A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial

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KEYWORDS
Stent, eluting stent, everolimus, randomized trial.

Abstract

Background: Everolimus is a sirolimus analogue with similar efficacy in animal models, and has been previously successfully tested in humans using an erodable polymer.

Methods: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus eluting from a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Sixty patients were allocated to stent implantation with an everolimus-eluting stent (n=28) or an identical bare stent (n=32). Patients had either stable, unstable angina or silent ischaemia. Suitable lesions treated were single *de novo* native coronary lesions with 50-99% stenosis and could be covered by a 18 mm stent. The primary endpoint was in-stent late loss at 180 days, analysed on a per treatment basis. The major secondary endpoint was percent in-stent volume obstruction (%VO) as measured by intravascular ultrasound (IVUS) at 180 days. The clinical secondary endpoint was major adverse cardiac events (MACE) at 180 days.

Results: At 6 months, (matched pairs angiographic analysis), the in-stent late loss, percentage diameter stenosis and percentage of patients with binary restenosis were 0.10 mm, 16% and 0% respectively, in the everolimus arm (n=23), as compared with 0.87 mm, 39% and 25.9%, respectively in the bare stent arm (n=27, p<0.001 for late loss and diameter stenosis, p = 0.01 for restenosis). Significantly less neointimal hyperplasia was observed in the everolimus group compared to the bare stent group (10 ± 13 mm^3 vs 38 ± 19 mm^3, p<0.001) and similarly, less volume obstruction (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). A major adverse cardiac event occurred in 2 patients in the everolimus arm versus 6 in the bare stent arm.

Conclusion: Everolimus eluted from a durable polymer on a cobalt chromium stent effectively suppresses neointimal growth at 6 months compared to an identical bare stent.

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Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia[1,2].

Everolimus is an effective anti-proliferative agent[3]. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of mammalian Target Of Rapamycin (mTOR), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with its function. Disabling mTOR explains the cell cycle arrest at the late G1 stage caused by everolimus and sirolimus.

The feasibility of using everolimus on a drug eluting stent was determined by the FUTURE I trial[4]. This trial utilized an S-stent and bioabsorbable polymer system (both Biosensors International, Singapore) and confirmed the safety of the everolimus-eluting stent at 6 and 12 months. At 6 months, a 7.7% Major Adverse Cardiac Event (MACE) rate was observed with no thrombosis and no late incomplete apposition. The efficacy was demonstrated by significant reduction of in-stent tissue proliferation at 6 months: both angiographic in-stent late loss and IVUS% neointimal volume were reduced by 87%. No angiographic in-stent binary restenosis was observed in the everolimus-eluting stent arm. The 12 month FUTURE I results showed sustained safety and efficacy with no new MACE events, no aneurysms, no late stent malapposition, and no thrombosis observed between 6 and 12 months. Minimal Lumen Area and Luminal Volume Index were maintained up to 12 months and no in-stent binary restenosis was observed up to 12 months.

The SPIRIT First clinical trial represents the first clinical evaluation of the Guidant XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE™ V Everolimus Eluting CSS), to investigate the potential benefits of the local application of everolimus in a durable polymer in combination with a thin strut cobalt chromium stent.

Methods

Patient selection

This randomized single-blind trial was performed at 9 medical centers and enrolled patients from December 2003 to April 2004. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were aged above 18 years and had received a diagnosis of stable or unstable angina or silent ischaemia. Additional eligibility criteria were the presence of a single primary *de novo* coronary lesion that was 3.0 mm in diameter as assessed by on-line QCA, that could be covered by an 18 mm stent, a stenosis of between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of an unprotected left main coronary artery, an ostial location, located within 2 mm of a bifurcation, a lesion with moderate to heavy calcification, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, chromium, nickel, tungsten, everolimus, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated.

The Everolimus-eluting stent

The Guidant XIENCE™ V Everolimus Eluting CSS is comprised of the Guidant MULTI-LINK VISION® Stent and delivery system, and a drug eluting coating. The Guidant MULTI-LINK VISION® Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a nonerodable polymer (this drug layer was coated over another nonerodable polymer primer layer). This coating includes of acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimeter of stent surface area with no top coat polymer layer. The stent is designed to release approximately 70% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation[5]. Everolimus has received market approval in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria and prior to the procedure, patients were allocated through a telephone randomization service and assigned in a 1:1 ratio to either an everolimus eluting stent or bare metal stent. A single stent 3.0 mm in diameter, 18 mm long was used in the study.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the rated burst pressure. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was allowed with a balloon shorter than the implanted stent. In the event of a dissection occurring at the edge of the implanted stent, it was recommended that a single additional bare Guidant MULTI-LINK VISION® stent be implanted as animal data only on single everolimus stent implantation were available at the onset of the study; these patients were *a priori* excluded from the per-treatment analysis but are part of the acute success population. IVUS was performed after angiographically optimal stent placement had been obtained and was repeated if additional post-dilatation was performed.

Intravenous boluses of heparin were administered according to local standard practice. Treatment with aspirin, at a minimum dose of 80 mg per day, was started at least 24 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 24 hours before the procedure, followed

by 75 mg daily for three months. Treatment with ticlopidine was permitted in case of clopidogrel hypersensitivity. Device success was defined as a final in-stent diameter stenosis of less than 50 percent by QCA using the assigned device. Clinical success was defined as the successful implantation of any device, with stenosis of less than 50 percent of the vessel diameter by QCA and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and 6 months. Further evaluations will be performed at 9 months and 1 year, with annual evaluations out to 5 years. At outpatient visits, patients were asked specific questions about the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. They were also monitored for MACE. Angiographic and IVUS evaluations were performed at 6 months, and will be repeated at 1 year. Prior to performing a follow-up angiogram, the physician was required to record in the source documents whether a revascularization (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: computer-defined Minimal Luminal Diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis $\geq$50% at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as matched pairs in the manuscript and as unmatched pairs in the Appendix. Unmatched pairs data is most commonly presented and utilises the mean QCA results of all projections obtained. Matched pairs data is more accurate as it compares the same views post-procedure and at follow-up and uses only QCA data of identical projections.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array intravascular ultrasound using automated pullback at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm. The Stent Volume (SV) and Lumen Volume (LV) were calculated according to Simpson's rule. The intra-stent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intra-stent neointimal volume/stent volume*100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[6]. Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.

Study endpoints

The primary angiographic endpoint was in-stent luminal late loss, as determined by quantitative angiography. Secondary endpoints (QCA and IVUS) at 6 months and 1 year included the in-stent and in-segment late loss, angiographic binary restenosis rate, percentage diameter stenosis; and in-stent percentage volume obstruction. In-stent was defined as within the margins of the stent while in-segment was defined as located either within the margins of the stent or 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the follow-up and post-procedure minimum luminal diameter. Secondary clinical endpoints were a composite of major cardiac events, including cardiac death, Q-wave or non-Q-wave myocardial infarction, clinically driven surgical or percutaneous revascularization of the target lesion (MACE) or vessel (Target Vessel Failure) at 30 days, 6 months, 9 months, and annually up to 5 years after the index procedure; and acute device, procedure and clinical success. All deaths that could not be clearly attributed to another cause were considered cardiac deaths. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase-MB, in the absence of new Q waves on electrocardiography.

The endpoints were adjudicated by an independent clinical events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population which consisted of patients who had no bailout stenting and no major protocol deviations, as evaluated in a blinded manner. Acute success was analyzed on the entire patient population.

The sample size for the study was determined based on the primary endpoint of in-stent late loss at 180 days and on the following assumptions: a single comparison of active to uncoated; one-tailed t-test, unequal and unknown variances in the two groups being compared; α=0.05; true mean difference between the bare stent group and the treatment group of 0.48 mm. This assumption was made based on the results of the VISION Registry (mean late loss=0.83 mm)[7], SIRIUS trial (mean late loss=0.17 mm)[8] and TAXUS IV trial (mean late loss=0.39 mm)[9]. (Assume the true mean late loss for the treatment group is 0.35 mm, the difference between the bare stent group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm). The standard deviation was assumed to be 0.56 mm in the bare stent group and 0.38 mm in the treatment group (based on the results of the VISION Registry study and SIRIUS trial); approximately 20% rate of lost to follow-up or dropout; approximate-

ly 10% of patients with bailout stents. Given the above assumptions, 30 patients per arm (with the analysis of 22 evaluable patients per arm) will provide 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) would provide more than 96% power.

Binary variables were compared using Fisher's Exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon Rank-Sum test, except for the primary endpoint which was evaluated with a one sided *t*-test. Final 6-month results are presented in the manuscript, while the Appendix contains results that were available at the time that the 180-day report was prepared.

Results

Patient characteristics

Between December 2003 and April 2004, 28 patients were randomly assigned to receive the everolimus-eluting stent, and 32 were assigned to receive the bare stent. As defined in the protocol, all results (except acute success) are presented for the per-treatment population (27 patients in the everolimus group, and 29 patients in the bare stent group, Figure 1). In the everolimus group there was one bailout procedure, and in the bare stent group there were two bailout procedures and one major protocol deviation (the patient was on the heart transplant waiting list). With the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus group, the two groups were similar with respect to clinical variables examined (Table 1).

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus stent (n = 27)	Bare stent (n = 29)	All patients (n = 56)
Age(yrs)	64 ± 10	61 ± 9	63 ± 9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring medication (%)	70	41	55
Hyperlipidemia requiring medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left anterior descending	48	45	46
Left circumflex	22	21	21
RCA	30	34	32
AHA / ACC Lesion Class (%)**			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference Vessel Diameter (mm ± SD)	2.61 ± 0.40	2.71 ± 0.28	2.66 ± 0.34
Lesion length (mm ± SD)	10.1 ± 2.6	10.9 ± 3.3	10.5 ± 3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

** AHA / ACC = American Heart Association / American College of Cardiology

FIGURE 1

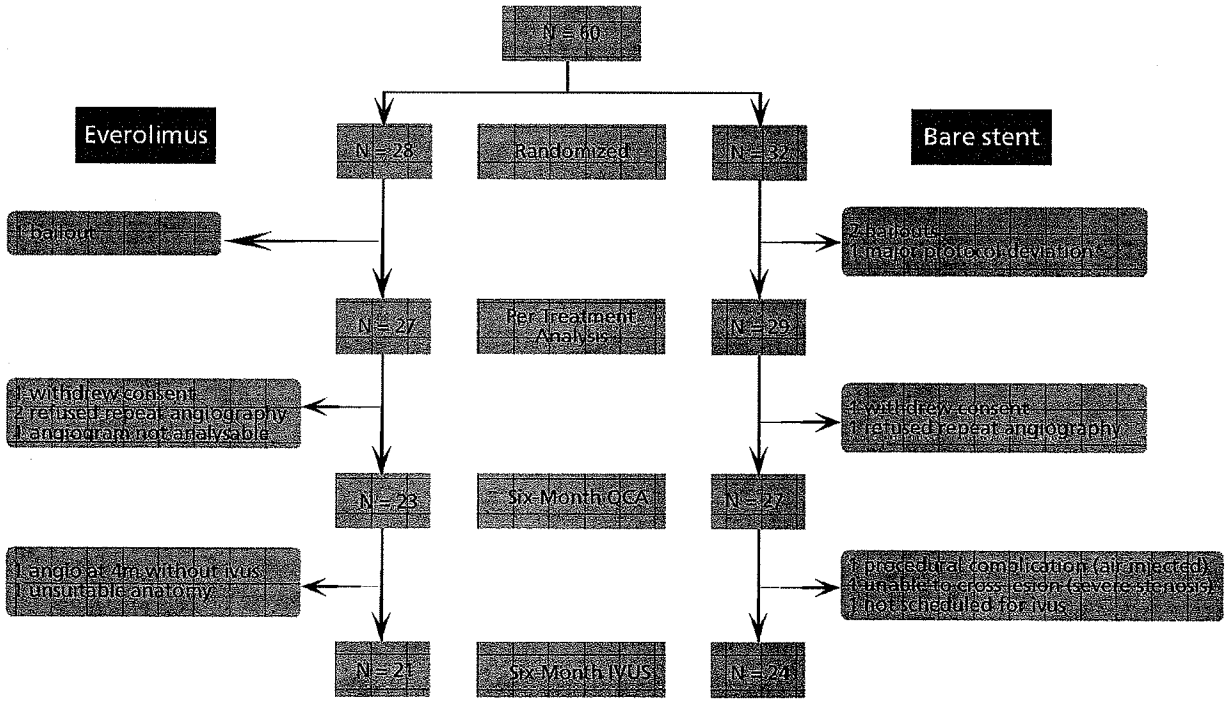

Fig. 1: Flowchart of patients

Procedural characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Glycoprotein IIb/IIIa inhibitors, used at the investigators' discretion, were administered to 7.4% of the patients in the everolimus group and 3.4% of those in the bare stent group. The two groups did not differ significantly with respect to the rate of device success (96.4% in the everolimus group and 93.8% in the bare stent group) or clinical success (96.4% in the everolimus group and 100% in the bare stent group).

Quantitative coronary angiography analysis

Angiographic data at 6 months were available for 50 of the 56 analysable patients (89.3%). The mean reference diameter of the target vessel, the mean length of the lesion at baseline, the reference vessel diameter and mean MLD of the stented segment were similar in the two groups (Tables 1 and 2). At six months, with matched pairs analysis, the mean MLD of the stented segment was significantly greater in the everolimus group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were 0.10 mm, 16%, and 0%, respectively, in the everolimus group, as compared with 0.87 mm, 39%, and 25.9%, respectively, in the bare stent group ($p<0.001$ for late loss and diameter stenosis, $p=0.01$ for restenosis). Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 and Figure 3 show the results of sub-segmental quantitative angiographic analyses for matched pairs. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus group than in the bare stent group ($p<0.01$ for proximal and $p=0.04$ for distal). The late luminal loss in the stented segment was significantly less in the everolimus group than in the bare stent group ($p \leq 0.001$).

Intravascular ultrasound evaluation

At six months follow-up, intravascular ultrasound evaluation showed no significant differences between the two groups with respect to the volume of the stent or the vessel volume (Table 3). Significantly

FIGURE 2

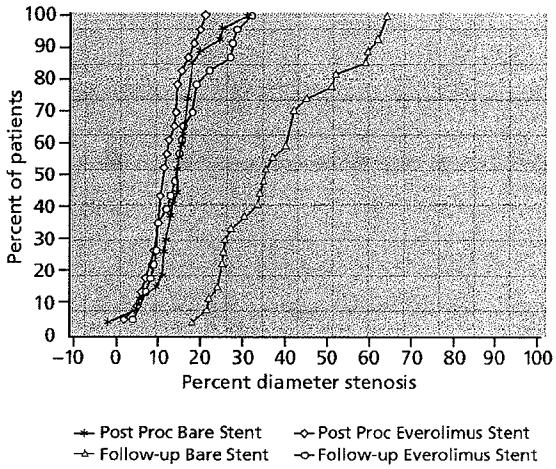

Fig. 2: Cumulative frequency of stenosis (in-stent) immediately after stenting and at six months

FIGURE 3

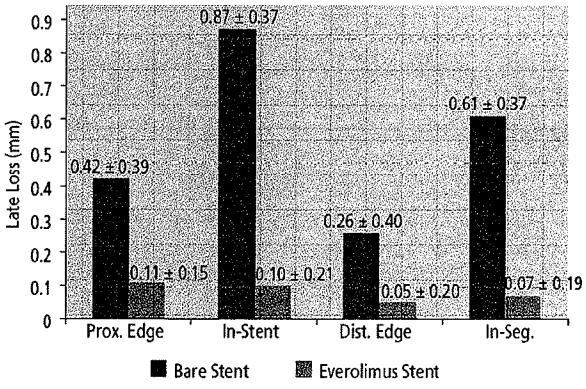

Fig. 3: Comparison of in-segment / in-stent late loss

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Matched Pairs).

	Proximal edge			In-stent			Distal edge			In-segment analysis		
	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value
Reference Vessel Diameter (mm)												
After procedure	2.80 ± 0.33	3.04 ± 0.38	0.06*	2.71 ± 0.28	2.89 ± 0.35	0.11*	2.64 ± 0.30	2.80 ± 0.39	0.21*	2.65 ± 0.30	2.84 ± 0.41	0.10*
At 6 months	2.78 ± 0.32	2.67 ± 0.40	0.22*	2.70 ± 0.31	2.58 ± 0.37	0.25*	2.61 ± 0.37	2.46 ± 0.36	0.19*	2.61 ± 0.36	2.59 ± 0.36	0.89*
Minimal Luminal Diameter (mm)												
After procedure	2.56 ± 0.44	2.61 ± 0.45	0.79*	2.38 ± 0.25	2.45 ± 0.31	0.50*	2.23 ± 0.41	2.26 ± 0.45	0.77*	2.11 ± 0.35	2.14 ± 0.40	1.00*
At 6 months	2.45 ± 0.46	2.19 ± 0.49	0.04*	2.28 ± 0.33	1.58 ± 0.41	< 0.001*	2.18 ± 0.38	2.00 ± 0.45	0.21*	2.04 ± 0.40	1.54 ± 0.41	< 0.001*
Late Loss (mm)	0.11 ± 0.15	0.42 ± 0.39	<0.01*	0.10 ± 0.21	0.87 ± 0.37	< 0.001***	0.05 ± 0.20	0.26 ± 0.40	0.04*	0.07 ± 0.19	0.61 ± 0.37	< 0.001*
Diameter Stenosis (%DS)												
After procedure	9 ± 11	14 ± 9	0.07*	12 ± 5	15 ± 6	0.05*	16 ± 10	20 ± 10	0.16*	20 ± 8	24 ± 9	0.05*
At 6 months	12 ± 12	17 ± 17	0.26*	16 ± 8	39 ± 14	< 0.001*	16 ± 10	19 ± 14	0.82*	22 ± 11	41 ± 14	< 0.001*
Binary Restenosis Rates	4.3%	3.7%	1.00**	0.0%	25.9%	0.01**	0.0%	7.4%	0.49**	4.3%	33.3%	0.01**

* two-sided Wilcoxon rank sum test ** two-sided Fisher's Exact test *** One-sided t-test † Fisher's Exact test

Table 3. IVUS measurements at 6 month follow-up.

	Everolimus- (n = 21*)	Bare (n = 24*)	P-value
Vessel volume (mm^3)	291 ± 82	296 ± 73	0.64
Stent volume (mm^3)	134 ± 28	139 ± 33	0.69
In-stent neo-intimal volume (mm^3)	10 ± 13	38 ± 19	<0.001
Luminal volume (mm^3)	124 ± 32	100 ± 31	0.04
In-stent volume obstruction (%)**	8.0 ± 10.4	28.1 ± 14.0	<0.001

* This final table contains an additional 13 patients not included in the 180-day report prepared for the sponsor. In 8 patients (4 in each group), an imputed stent length of 18mm was used due to non-continuous pullback. In a further 5 patients (all bare stent group) results were unavailable at the time of the 180-day report. (see Appendix)

** In-stent volume obstruction = 100*
(In-stent neo-intimal volume / Stent volume)

less neointimal hyperplasia was observed in the everolimus-stent group compared to the bare-stent group (10 ± 13 vs. 38 ± 19 mm^3, p<0.001) and similarly, significantly less volume obstruction, (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). Figure 4 is a cumulative curve of percentage volume obstruction. No in-stent volume obstruction was detected in almost half of the patients in the everolimus-stent group, whereas in the bare stent group, some degree of obstruction by neointima was present in all patients (Figure 4). No evidence of an "edge effect," aneurysm formation, in-stent thrombosis, persistent dissection or late incomplete apposition were observed.

FIGURE 4

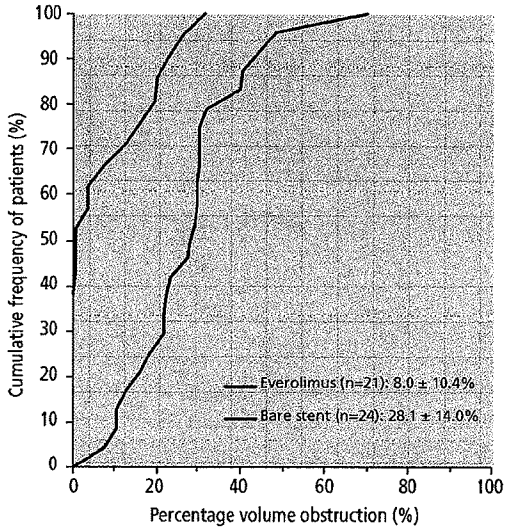

Fig. 4: Percentage in-stent volume obstruction versus cumulative frequency of patients. Values are expressed as mean ± standard deviation for each group.

Major adverse cardiac events

Major adverse cardiac events are listed in Table 4. There was one Q-wave myocardial infarction in the everolimus group in a patient who underwent additional revascularization for angina in a non-target vessel 18 days after the study procedure and suffered thrombosis of this non-study stent 12 days later. The everolimus stent was patent with no evidence of thrombus at the time of the thrombotic occlusion of the non study stent. One patient in the everolimus arm underwent a clinically driven target lesion revascularization at 3 weeks for symptomatic persistent dissection at the proximal edge left untreated at the time of the procedure. There were no clinically driven target revascularizations in the everolimus group for restenosis. There were six clinically driven target lesion revascularizations in the bare stent group, five were treated percutaneously for restenosis and the sixth by bypass surgery. No adverse effects were attributable to everolimus or the polymer coating of the stents.

Table 4. Hierarchical major adverse cardiac events at 180 days in per-treatment population*.

Event**	Everolimus stent n = 26	%	Bare stent n = 28	%
Cardiac death	0	0	0	0
Myocardial infarction				
Q-wave	1‡	3.8	0	0
Non-Q-wave	0	0	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	1 §	3.8	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	2	7.7	6	21.4
Major adverse cardiac events	2	7.7	6	21.4

* One patient in each group withdrew consent after treatment
** No statistical significance was detected between groups for all endpoints tested.
‡ Q-wave MI due to thrombosis of a non-study stent in a non-target vessel.
§ Clinically driven TLR for persistent dissection proximal to the stent 3 weeks after the index procedure.

Discussion

The main finding of this randomized first-in-man study is that an everolimus-eluting stent coated with a durable polymer was associated with an in-stent angiographic late loss of 0.10 mm, significantly less than the corresponding bare cobalt chromium metal stent of 0.87 mm, which satisfied the primary endpoint of this trial and confirmed the efficacy of this system. Correspondingly, in-segment late loss was also significantly less in the everolimus-stent group.
Currently, two different drug-eluting systems (sirolimus and paclitaxel) are available. Although no published scientific comparative data is to date available, it appears that, from historical randomized trials, a difference of approximately 0.2 mm in-stent late loss exists between sirolimus and paclitaxel. Even if the impact of restenosis and MACE is currently unknown, some slight difference in restenosis rates and MACE can be expected. New devices should at least equal the incumbents in performance. This performance may be judged on late

loss, restenosis rate and / or the need for reintervention. With an in-stent late loss ranging from zero to 0.2 mm, it has been difficult to find a compound with the same efficacy, without resorting to the -limus family (Figure 5). With the sirolimus molecule being rather large and complex, it is therefore not surprising that major pharmaceutical companies have thoroughly explored its numerous analogues in order to develop a suitable competitor to sirolimus. The drug used in this study, everolimus differs from sirolimus by a substitution of a hydrogen radical/side-branch with a methyl sidechain.

FIGURE 5

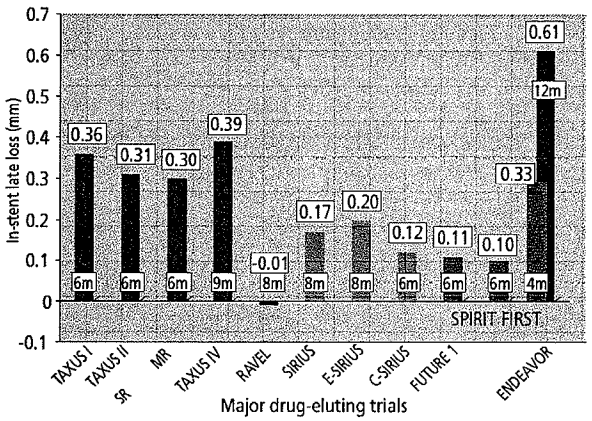

Fig. 5: Comparison of in-stent late loss from drug-eluting trials.

The reason for developing new compounds is to improve on the side effects of the existing compounds such as delayed healing with re-endothelialization and fibrin[11], early[12] and late stent thrombosis[13]. The success of the device lies in its three components - the drug, the polymer properties and the stent. The use of a sirolimus analogue is not in itself a guarantee of success since some of them have intrinsically, a potency in inhibition of up to 100 times less (e.g. tacrolimus), and some other analogues with equal *in vitro* inhibitory effects nevertheless fail to equally inhibit neointimal growth *in vivo*, because their duration of elution was suspected to be too short. However it has already been demonstrated that everolimus in clinical trials using a bioerodable polymer with a slower elution profile than sirolimus is effective in reducing late loss to below 0.2 mm[4]. Therefore the remaining challenge was to establish whether everolimus eluted from a durable polymer was also efficient and is addressed in this report.

Although the 6-month results are promising, one year angiographic and IVUS follow-up results are awaited to confirm the long-term results of this device in light of recent findings regarding an increasing late loss seen with other devices over time.

At the time of the publication of RAVEL, it was argued that the restenosis rate of the bare stent was excessively high at 26%. Similarly, in the present trial the restenosis rate in the bare stent arm was 25.9%. Nevertheless, it must be emphasized that in both cases these restenosis rates correspond to the value predicted and derived from multivariate analyses including as determinant parameters vessel size, MLD post, incidence of LAD disease and diabetics. Of interest, the late loss of the bare stent groups in RAVEL and this study were similar, corresponding to their restenosis rates. This is at variance with the VISION registry, and publications on stent strut thickness, but may be explained by the mismatch in stent size and reference diameter.

This study was powered for late loss and not for clinical events, and it was not surprising that the 3 fold reduction in events failed to be statistically significant. At the time of trial design, safety studies with overlapping eluting-stents in animal models had not been completed, requiring the use of bare stents for bailout. As a result of this confounder, these patients were *a priori* excluded from the per-treatment analysis. This study was however designed as a first in man trial with everolimus on an untested new durable polymer in combination with a cobalt chromium stent.

Acknowledgements

The authors would like to acknowledge the invaluable assistance of Susan Veldhof, RN, Cecile Dorange, MSc, Sophie Henry, MSEE from Guidant Europe, Diegem, Belgium for the conduct and reporting of this study.

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Appendix

Sponsor: Guidant Corporation, Santa Clara, California, USA.

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Executive Committee: P.W. Serruys (Principal Investigator and Chairman, Rotterdam, The Netherlands); Gary Johnson (Vice President of Regulatory Affairs/Clinical Research, Guidant Corporation); Stan Fink (Director of Clinical Research USA, Guidant Corporation).

Data Safety Monitoring Board (DSMB) - J.G.P. Tijssen, Amsterdam, The Netherlands; F.W.A. Verheugt, Nijmegen, The Netherlands; W. Wijns, Aalst, Belgium.

Clinical Events Committee (CEC) - J. Vos, Amphia Ziekenhuis, Breda, The Netherlands; B.J.W.M. Rensing, Sint Antonius Ziekenhuis, Nieuwegein, the Netherlands; C. Hanet, Clinique Universitaire de Saint-Luc, Brussels, Belgium.

Data management - Angiographic and IVUS core laboratories: Cardialysis BV, Rotterdam, The Netherlands; Data Coordination Centre and Site Monitoring: Guidant Europe, Diegem, Belgium.

The following investigators and institutions participated in the SPIRIT First trial:

Clinical sites: J.J. Piek, Academisch Medisch Centrum, Amsterdam, The Netherlands (18 patients); F.J. Neumann, Herzzentrum, Bad Krozingen, Germany (14 patients); P.W. Serruys, Thoraxcentre, Erasmus Medical Centre, Rotterdam, The Netherlands (5 patients); M. Wiemer, HZ Herzzentrum, Bad Oeynhausen, Germany (5 patients); A. Zeiher, Uni. Klinikum Frankfurt, Frankfurt, Germany (4 patients); E. Grube, Heart Center Siegburg, Siegburg, Germany (4 patients); J. Haase, Red Cross Hospital, Frankfurt, Germany (4 patients); L. Thuesen, Skejby Sygehus, Aarhus, Denmark (4 patients); C. Hamm, Kerckhoff Klinik, Bad Nauheim, Germany (2 patients).

Table A2. Appendix: results of intra vascular ultra sound analysis as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Everolimus (n = 17)	Bare (n = 15*)	P-value
Vessel volume (mm^3)	299 ± 87	284 ± 77	0.76
Stent volume (mm^3)	138 ± 30	139 ± 39	1.00
In-stent neo-intimal volume (mm^3)	11.2 ± 14.0	41.4 ± 20.1	<0.001
Luminal volume (mm^3)	126 ± 35	98 ± 34	0.06
In-stent volume obstruction (%)	8.6 ± 10.7	29.0 ± 13.9	<0.001

Table A1. Appendix: results of sub-segmental quantitative coronary angiographic analysis (Unmatched Pairs) as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Proximal edge			In-stent			Distal edge			In-segment analysis		
	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value
Minimal luminal diameter (mm)												
After procedure	2.49 ± 0.44	2.57 ± 0.39	0.44*	2.34 ± 0.26	2.42 ± 0.31	0.41*	2.18 ± 0.44	2.25 ± 0.42	0.67*	2.07 ± 0.37	2.14 ± 0.37	0.74*
At 6 months	2.45 ± 0.46	2.19 ± 0.50	0.05*	2.28 ± 0.33	1.58 ± 0.42	<0.001*	2.18 ± 0.38	1.99 ± 0.46	0.19*	2.04 ± 0.40	1.53 ± 0.41	<0.001*
Late loss (mm)	0.10 ± 0.17	0.38 ± 0.38	0.01*	0.10 ± 0.23	0.84 ± 0.36	<0.001***	0.07 ± 0.20	0.26 ± 0.41	0.14*	0.09 ± 0.20	0.60 ± 0.36	<0.001*
Diameter stenosis (%DS)												
After procedure	10 ± 10	15 ± 9	0.13*	12 ± 4	15 ± 6	0.02*	17 ± 10	19 ± 9	0.39*	21 ± 8	24 ± 8	0.14*
At 6 months	12 ± 12	18 ± 17	0.21*	16 ± 8	39 ± 14	<0.001*	16 ± 10	20 ± 14	0.67*	22 ± 11	41 ± 14	<0.001*
Binary restenosis rates	4.3%	3.8%	1.00**	0.0%	26.9%	0.01**	0.0%	7.7%	0.49**	4.3%	34.6%	0.01**

* Two-sided Wilcoxon rank sum test ** Two-sided Fisher's Exact test *** One-sided t-test

ORIGINAL CONTRIBUTION

Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease

A Randomized Trial

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Context A thin, cobalt-chromium stent eluting the antiproliferative agent everolimus from a nonadhesive, durable fluoropolymer has shown promise in preliminary studies in improving clinical and angiographic outcomes in patients with coronary artery disease.

Objective To evaluate the safety and efficacy of an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent.

Design, Setting, and Patients The SPIRIT III trial, a prospective, randomized, single-blind, controlled trial enrolling patients at 65 academic and community-based US institutions between June 22, 2005, and March 15, 2006. Patients were 1002 men and women undergoing percutaneous coronary intervention in lesions 28 mm or less in length and with reference vessel diameter between 2.5 and 3.75 mm. Angiographic follow-up was prespecified at 8 months in 564 patients and completed in 436 patients. Clinical follow-up was performed at 1, 6, 9, and 12 months.

Interventions Patients were randomized 2:1 to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333).

Main Outcome Measures The primary end point was noninferiority or superiority of angiographic in-segment late loss. The major secondary end point was noninferiority assessment of target vessel failure events (cardiac death, myocardial infarction, or target vessel revascularization) at 9 months. An additional secondary end point was evaluation of major adverse cardiac events (cardiac death, myocardial infarction, or target lesion revascularization) at 9 and 12 months.

Results Angiographic in-segment late loss was significantly less in the everolimus-eluting stent group compared with the paclitaxel group (mean, 0.14 [SD, 0.41] mm vs 0.28 [SD, 0.48] mm; difference, −0.14 [95% CI, −0.23 to −0.05]; $P \leq .004$). The everolimus stent was noninferior to the paclitaxel stent for target vessel failure at 9 months (7.2% vs 9.0%, respectively; difference, −1.9% [95% CI, −5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P < .001$). The everolimus stent compared with the paclitaxel stent resulted in significant reductions in composite major adverse cardiac events both at 9 months (4.6% vs 8.1%; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P = .03$) and at 1 year (6.0% vs 10.3%; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P = .02$), due to fewer myocardial infarctions and target lesion revascularization procedures.

Conclusions In this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00180479

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By enlarging the arterial lumen and sealing dissection planes, stent implantation relieves coronary flow obstruction at the site of atherosclerotic disease. However, injury to the tunica media results in excessive neointimal hyperplasia in approximately 20% to 30% of patients treated with bare-metal stents, which results in recurrent ischemia often necessitating rehospitalization for repeat percutaneous coronary intervention or coronary artery bypass graft surgery.[1] Drug-eluting stents combine the mechanical scaffolding properties of metallic stents with the site-specific delivery of an antiproliferative agent designed to inhibit vascular responses to arterial injury, thereby reducing restenosis. The polymer-regulated, site-specific delivery of paclitaxel and sirolimus have been shown to inhibit tissue growth after coronary stent implantation and to improve long-term event-free survival compared with bare-metal stents.[2,3] However, restenosis still occurs, and the incidence of stent thrombosis, especially after

For editorial comment see p 1952.

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the first year of implantation, is increased with these drug-eluting stents compared with their bare-metal counterparts,[4,5] likely due to delayed and incomplete endothelialization.[6,7]

Newer drug-eluting stents are being designed with the goal of enhanced safety, efficacy, or both compared with previous devices. Everolimus, a semisynthetic macrolide immunosuppressant, is an analogue of rapamycin, which binds to cytosolic FKBP12 and subsequently to the mammalian target of rapamycin, thereby blocking the stimulatory effects of growth factors and cytokines, which are released after vascular injury. As a result, cell cycle progression is blocked between the G1 and S phases, inhibiting smooth muscle cell proliferation.[8]

Everolimus has been shown to prevent cardiac allograft vasculopathy,[9] which histologically resembles the neointimal hyperplasia that develops after coronary stent implantation.[10] An everolimus-eluting stent has been designed in which the drug is released from a thin (7.8-μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0032-in [0.0813-mm] strut thickness), flexible cobalt-chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared with sirolimus-eluting and paclitaxel-eluting stents.[11] Following favorable results with this device in 1 small and 1 moderate-sized randomized study in Europe,[12,13] the large-scale SPIRIT III trial was performed to evaluate the everolimus-eluting stent in comparison to a widely used paclitaxel-eluting stent in patients with coronary artery disease.

METHODS

Study Population, Device Description, and Protocol

SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1002 patients with either 1 or 2 de novo native coronary artery lesions (maximum 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the polymer-based everolimus-eluting stent (XIENCE V; Abbott Vascular, Santa Clara, California) or the polymer-based paclitaxel-eluting stent (TAXUS EXPRESS2; Boston Scientific, Natick, Massachusetts). Patients aged 18 years or older with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention were considered for enrollment.

Clinical exclusion criteria included percutaneous intervention in the target vessel either prior to or planned within 9 months after the index procedure; intervention in a nontarget vessel within 90 days prior to or planned within 9 months after the index procedure; prior coronary brachytherapy at any time; acute or recent myocardial infarction with elevated cardiac biomarker levels; left ventricular ejection fraction less than 30%; prior or planned organ transplantation; current or planned chemotherapy for malignancy; known immunologic or autoimmune disease or prescribed immunosuppressive medication; use of chronic anticoagulation; contraindications or allergy to aspirin, heparin, and bivalirudin, thienopyridines, everolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoropolymers, or to iodinated contrast that cannot be premedicated; elective surgery planned within 9 months after the procedure, necessitating antiplatelet agent discontinuation; platelet count less than 100 000 cells/μL or greater than 700 000 cells/μL, white blood cell count less than 3000 cells/μL, serum creatinine level greater than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4), or dialysis or liver disease; recent major bleeding, hemorrhagic diathesis, or objection to blood transfusions; stroke or transient ischemic attack within 6 months; comorbid conditions that limit life expectancy to less than 1 year or that could affect protocol compliance; positive pregnancy test result, lactation, or planned pregnancy within 1 year after enrollment; and participation in another investigational study that has not yet reached its primary end point. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed written informed consent.

Prior to catheterization, an electrocardiogram was performed, creatine phosphokinase and isoenzyme levels were measured, and 300 mg or more of aspirin was administered. A 300-mg or greater oral dose of clopidogrel was recommended preprocedure and required in all cases within 1 hour after stent implantation. Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin per standard of care, and use of glycoprotein IIb/IIIa inhibitors was per operator discretion. Angiographic eligibility was assessed following mandatory predilatation. The reference vessel diameter of all study lesions was required to be between 2.5 mm and 3.75 mm, and the lesion length was required to be 28 mm or less, both by visual assessment, representing the on-label lesion dimensions for which the paclitaxel-eluting stent has been approved by the US Food and Drug Administration (FDA) for use in the United States. Other angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with either side branch more than 50% stenosed or more than 2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation or calcification, or thrombus; lesion located within a bypass graft conduit; diameter stenosis less than 50% or 100%; or the presence of lesions with greater than 40% stenosis within the target vessel or likelihood that additional percutaneous intervention would be required within 9 months.

Following confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of 3 and 6 patients using an automated voice response system, stratified by the presence of diabetes, planned dual-vessel treatment, and study site. For this trial everolimus-eluting stents were available in 2.5-, 3.0-, and 3.5-mm diameters, and in 8-, 18-, and 28-mm lengths. The full range of US-manufactured paclitaxel-eluting stents were available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length. An appropriate-length stent was selected sufficient to cover approximately 3 mm of nondiseased tissue on either side of the lesion. In patients receiving multiple

stents for a single lesion, 1 to 4 mm of stent overlap was recommended. Additional study stents were permitted for edge dissections greater than type C or otherwise suboptimal results, and postdilation was at operator discretion.

Following the procedure, an electrocardiogram was performed and cardiac enzyme levels were measured. The protocol recommended that patients receive aspirin (≥80 mg/d) indefinitely and clopidogrel (75 mg/d) for a minimum of 6 months. Clinical follow-up was scheduled at 30 (±7) days, 180 (±14) days, 240 (±28) days, 270 (±14) days, 365 (±28) days, and then yearly (±28 days) through 5 years. Although the operators were by necessity unblinded during the stent implantation procedure, the patient and staff involved in follow-up assessments remained blinded through the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol-specified angiographic follow-up was scheduled at 240 (±28) days in the first 564 patients enrolled. Among these patients, intravascular ultrasound immediately following stent implantation and at follow-up was intended in 240 patients at selected sites.

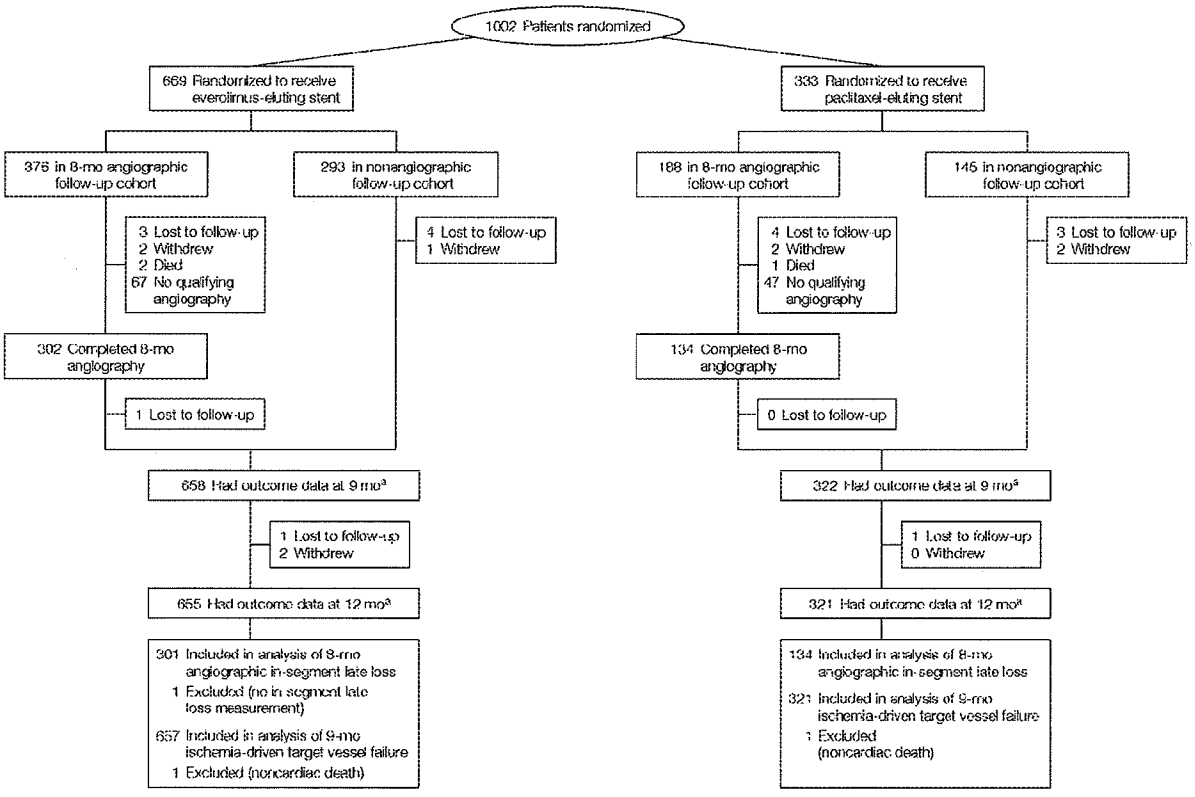
Data Management

Independent study monitors verified 100% of case report form data on-site. Data were stored in a database maintained by Abbott Vascular. All major adverse cardiac events were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation. A second clinical events committee blinded to randomization performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium definitions.[14] A data and safety monitoring board periodically reviewed blinded safety data, each time recommending that the study continue without modification. Independent core angiographic and intravascular ultrasound analyses were performed by technicians blinded to treatment assignment and clinical outcomes using validated methods as previously described.[15,16]

End Points and Definitions

The primary end point was in-segment late loss at 240 days (defined as the difference in the minimal luminal diameter assessed immediately after the pro-

Figure 1. Patient Flow and Follow-up in the SPIRIT III Trial



Prior to the 1-year follow-up period, 14 of 669 patients (2.1%) randomized to receive the everolimus-eluting stent either withdrew (n=5) or were lost to follow-up (n=9), and 12 of 333 patients (3.6%) randomized to receive the paclitaxel-eluting stent either withdrew (n=4) or were lost to follow-up (n=8).
[a]Nine-month follow-up was performed at 270 (±14) days; 12-month follow-up, at 365 (±28) days.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent
Demographics, No./total (%)	669	332
Age, mean (SD), y	63.2 (10.5)	62.8 (10.2)
Men	469/669 (70.1)	218/332 (65.7)
Hypertension	510/669 (76.2)	245/331 (74.0)
Hypercholesterolemia	489/659 (74.2)	233/326 (71.5)
Diabetes mellitus		
Any	198/669 (29.6)	92/330 (27.9)
Requiring insulin	52/669 (7.8)	18/330 (5.5)
Current smoker	154/659 (23.4)	73/324 (22.5)
Prior myocardial infarction	130/652 (19.9)	59/327 (18.0)
Unstable angina	123/657 (18.7)	82/327 (25.1)
Target vessel, No./total (%)	772	383
Left anterior descending	317/768 (41.3)	164/382 (42.9)
Left circumflex	212/768 (27.6)	108/382 (28.3)
Right coronary	238/768 (31.0)	109/382 (28.5)
Left main, protected	1/768 (0.1)	1/382 (0.3)
Target lesion, mean (SD)	772	383
Reference vessel diameter, mm	2.77 (0.45)	2.76 (0.46)
Minimal luminal diameter, mm	0.82 (0.41)	0.83 (0.40)
Diameter stenosis, %	70.0 (13.3)	69.4 (13.6)
Lesion length, mm	14.7 (5.6)	14.7 (5.7)

cedure and at angiographic follow-up, measured within the margins, 5 mm proximal and 5 mm distal to the stent). To avoid interlesion clustering of restenosis in patients receiving stents for multiple lesions[17] (which would have required correction with multilevel generalized estimating equations), the protocol specified that for patients in whom 2 lesions were treated a single lesion (the analysis lesion) would be randomly selected by computer for analysis of late loss. All randomized lesions were included in the analyses for all other angiographic end points.

The major secondary end point was ischemia-driven target vessel failure at 270 days, defined as the composite of cardiac death (death in which a cardiac cause could not be excluded), myocardial infarction (Q-wave or non–Q-wave), and ischemia-driven target vessel revascularization by either percutaneous coronary intervention or bypass graft surgery. Target vessel (or lesion) revascularization was considered to be ischemia-driven if associated with a positive functional study result, a target vessel (or lesion) diameter stenosis of 50% or greater by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis of 70% or greater with or without documented ischemia.

An additional prespecified secondary end point included major adverse cardiac events at 9 months and 1 year, defined as the composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization. Myocardial infarction was defined either as the development of new pathologic Q waves 0.4 seconds or longer in duration in 2 or more contiguous leads or as an elevation of creatine phosphokinase levels to more than 2 times normal with positive levels of creatine phosphokinase MB. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion or, in the absence of angiography, as any unexplained death or acute myocardial infarction with ST-segment elevation or new Q waves in the distribution of the target lesion occurring within 30 days. Binary restenosis was defined as 50% or greater diameter stenosis of the treated lesion at angiographic follow-up. Other angiographic and intravascular ultrasound parameters were defined as previously described.[15,16]

Statistical Methods

The trial was powered for noninferiority for both the primary end point of in-segment late loss at 8 months among patients in the angiographic follow-up cohort, as well as the major secondary end point of ischemia-driven target vessel failure at 9 months in all enrolled patients. As agreed on with FDA, noninferiority for in-segment late loss would be declared if the upper limit of the 1-sided 97.5% confidence interval (CI) of the difference did not exceed a delta of 0.195 mm from the observed in-segment late lumen loss in the paclitaxel-eluting stent group, equivalent to a 1-sided test with $\alpha = .025$. Assuming a mean late loss of 0.24 (SD, 0.47) mm for both stents, with angiographic follow-up performed in 338 everolimus-eluting stent and 169 paclitaxel-eluting stent analysis lesions, the trial had 99% power to demonstrate noninferiority for in-segment late loss. Sequential superiority testing was prespecified if noninferiority for late loss was met. Noninferiority for ischemia-driven target vessel failure was declared if the upper limit of the 1-sided 95% CI of the difference did not exceed a delta of 5.5% from the observed paclitaxel-eluting stent control event rate. Assuming a target vessel failure rate of 9.4% for both stents, with 9-month clinical follow-up performed in 660 patients randomized to receive the everolimus-eluting stent and 330 to receive the paclitaxel-eluting stent, the trial had 89% power to demonstrate noninferiority for target vessel failure. Noninferiority for the prespecified powered primary as well as the major secondary end points had to be met for the trial to be considered successful, and as such both are considered coprimary end points.

Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean (SD) and were compared by *t* test. The statistical analysis plan prespecified that all primary and secondary analyses

would be performed in the intent-to-treat population, consisting of all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred prior to the follow-up windows were not included in the denominator for calculations of binary end points. Survival curves using all available follow-up data were also constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. Superiority testing was performed after demonstration of noninferiority for the primary and major secondary end points[18] and for all other secondary end points using a 2-sided $\alpha = .05$. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients and Enrollment

Between June 22, 2005, and March 15, 2006, 1002 patients were enrolled at 65 US sites and randomized to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333) (FIGURE 1). One patient in the paclitaxel group did not sign informed consent; thus, his or her data are unavailable. Baseline characteristics of the patients were well matched between the 2 groups (TABLE 1), except for slightly more unstable angina in the paclitaxel group ($P = .02$). The mean number of lesions stented was 1.2 (SD, 0.4) in each group; 2 lesions were treated in 15.4% of patients in each group, whereas the remainder had 1 lesion treated. Lesion characteristics as measured by quantitative coronary angiography were also similar between the 2 groups (Table 1).

Procedural Results and Angiographic Outcomes

As shown in TABLE 2, the total stent length per lesion was slightly greater in the everolimus group, likely due to the fewer stent lengths available for accurate lesion matching. Conversely, implantation pressure was slightly less in the group receiving everolimus stents. Other procedural variables were well matched between the groups. Acute postprocedure angiographic measures were also not significantly different between the 2 groups.

Angiographic follow-up at 8 months was completed in 77% of eligible patients (Figure 1). The primary end point of in-segment late loss in the analysis lesion was significantly less in the everolimus group compared with the paclitaxel group (0.14 [SD, 0.41] mm [n=301 lesions] vs 0.28 [SD, 0.48] mm [n=134 lesions]; difference, −0.14 [95% CI, −0.23 to −0.05]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .004$). In-stent late loss in the analysis lesion was also significantly less in the everolimus group (0.16 [SD, 0.41] mm vs 0.31 [SD, 0.55] mm; difference, −0.15 [95% CI, −0.25 to −0.04]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .006$). Similar results were found when all lesions were considered (Table 2). As a result, strong trends were present toward a reduction in binary in-stent and in-segment restenosis with the everolimus stent compared with the paclitaxel stent (Table 2). No aneurysms were present at 8 months in either group.

Intravascular Ultrasound Findings

Volumetric intravascular ultrasound data were available at 8 months in 101

Table 2. Procedural Results and Angiographic Outcomes

Result/Outcome	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent	P Value
Procedural variables, mean (SD)			
No. of patients	669	332	
No. of stents per patient	1.3 (0.6)	1.3 (0.5)	.27
No. of stents per lesion	1.2 (0.4)	1.1 (0.3)	.07
Maximum stent diameter per lesion, mm	3.0 (0.4)	3.0 (0.4)	>.99
Maximum stent to reference vessel diameter ratio	1.1 (0.1)	1.1 (0.1)	.56
Total stent length per lesion, mm	22.8 (8.4)	21.6 (7.8)	.02
Total stent to lesion length ratio	1.6 (0.5)	1.5 (0.5)	.01
Maximum pressure, atm	14.8 (2.9)	15.1 (2.6)	.049
Glycoprotein IIb/IIIa inhibitors used, No./total (%)	184/669 (27.5)	82/332 (24.7)	.36
Postprocedural angiographic results, mean (SD)			
No. of lesions	772	383	
Minimal luminal diameter, mm			
In-stent	2.71 (0.43)	2.74 (0.41)	.38
In-segment	2.37 (0.45)	2.36 (0.45)	.73
Diameter stenosis, %			
In-stent	0.3 (8.9)	−0.2 (9.9)	.37
In-segment	13.5 (7.6)	14.4 (7.1)	.06
Acute gain, mm			
In-stent	1.89 (0.48)	1.91 (0.47)	.56
In-segment	1.54 (0.51)	1.53 (0.50)	.62
8-mo angiographic follow-up, mean (SD)[a]			
No. of lesions	344	158	
Reference vessel diameter, mm	2.77 (0.43)	2.78 (0.42)	.84
Minimal luminal diameter, mm			
In-stent	2.56 (0.53)	2.45 (0.65)	.07
In-segment	2.22 (0.53)	2.12 (0.60)	.08
Diameter stenosis, %			
In-stent	5.9 (16.4)	10.3 (21.4)	.02
In-segment	18.8 (14.4)	22.8 (16.4)	.008
Late loss, mm			
In-stent	0.16 (0.41)	0.30 (0.53)	.002
In-segment	0.14 (0.39)	0.26 (0.46)	.003
Binary restenosis, No./total (%)			
In-stent	8/343 (2.3)	9/158 (5.7)	.06
In-segment	16/344 (4.7)	14/158 (8.9)	.07

[a] Analysis of all lesions.

lesions in the everolimus group and 41 in the paclitaxel group. The everolimus stent compared with the paclitaxel stent resulted in significantly less neointimal hyperplasia (10.13 [SD, 11.46] mm^3 vs 20.87 [SD, 31.51] mm^3, $P=.04$) and percent volume obstruction (6.9% [SD, 6.4%] vs 11.2% [SD, 9.9%], $P=.01$). Paired immediate postprocedure and follow-up intravascular ultrasound studies were available in 90 lesions in the everolimus group and 43 in the paclitaxel group. Comparing the everolimus and paclitaxel stents, there were no significant differences detected in the rates of incomplete stent apposition either at the completion of the procedure (34.4% vs 25.6%, respectively; $P=.33$) or at 8 months (25.6% vs 16.3%, $P=.27$). Late acquired incomplete stent apposition was infrequent in both groups (1.1% vs 2.3%, $P=.54$).

Clinical Outcomes

At 30 days there tended to be fewer myocardial infarctions among the patients randomized to receive the everolimus stent compared with the paclitaxel stent (7/667 patients [1.0%] vs 9/330 [2.7%], respectively; relative risk, 0.38 [95% CI, 0.14 to 1.02]; $P=.06$), with comparable rates of cardiac death (0% in both groups) and target lesion revascularization (3/667 patients [0.4%] vs 1/330 [0.3%], respectively; relative risk, 1.48 [95% CI, 0.15 to 14.21]; $P>.99$). At 9 months, everolimus stents compared with paclitaxel stents were noninferior for the major secondary end point of ischemia-driven target vessel failure (47/657 patients [7.2%] vs 29/321 [9.0%], respectively; difference, −1.9% [95% CI, −5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P_{noninferiority}<.001$; $P_{superiority}=.31$). A nonsignificant trend was also present at 1 year for a 24% reduction in target vessel failure in patients randomized to receive everolimus stents rather than paclitaxel stents (56/653 patients [8.6%] vs 36/320 [11.3%], respectively; relative risk, 0.76 [95% CI, 0.51 to 1.13]; $P=.20$). Use of the everolimus stent compared with the paclitaxel stent resulted in significant reductions in the secondary end point of composite major adverse cardiac events, both at 9 months (30/657 patients [4.6%] vs 26/321 [8.1%]; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P=.03$) and at 1 year (39/653 patients [6.0%] vs 33/320 [10.3%]; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P=.02$).

As shown in TABLE 3, there were no significant differences between the everolimus stent and the paclitaxel stent in the 1-year rates of death (all cause, cardiac, or noncardiac) or of myocardial infarction (all, Q-wave, or non–Q-wave). Similarly, there were no significant differences between the 2 devices in the rates of stent thrombosis, either early (≤30 days) or late (>30 days), whether analyzed by the prespecified protocol definition or by post hoc Academic Research Consortium definitions. There were also no statistically significant differences in the rates of target lesion revascularization, target vessel revascularization, or target vessel failure between the 2 stents at 1 year. As shown in FIGURE 2, the difference between the hazard curves for major adverse cardiac events became apparent in the early postprocedural period due to fewer myocardial infarctions with the everolimus stent, and then spread further between 6 and 12 months due to fewer target lesion revascularization procedures with the everolimus stent. Of the 15 and 12 patients in the everolimus and paclitaxel groups who had a protocol-defined ischemic target lesion revascularization event by 1 year, 5 and 4 patients, respectively (33.3% in each group) underwent revascularization solely on the basis of a diameter stenosis greater than 70% demonstrated by quantitative coronary angiography. At 365 days, aspirin was being taken by 94.9% and 92.4%

Table 3. Clinical Outcomes at 1 Year

Outcome	No./Total (%) Everolimus-Eluting Stent (n = 655)	No./Total (%) Paclitaxel-Eluting Stent (n = 321)	P Value
Death	8/655 (1.2)	4/321 (1.2)	>.99
Cardiac	5/655 (0.8)	3/321 (0.9)	.72
Noncardiac	3/655 (0.5)	1/321 (0.3)	>.99
Myocardial infarction[a]	18/653 (2.8)	13/320 (4.1)	.33
Q-wave	2/653 (0.3)	1/320 (0.3)	>.99
Non–Q-wave	16/653 (2.5)	12/320 (3.8)	.31
Death or myocardial infarction	24/654 (3.7)	16/321 (5.0)	.39
Cardiac death or myocardial infarction[a]	22/653 (3.4)	15/320 (4.7)	.37
Stent thrombosis			
Protocol definition	5/647 (0.8)	2/317 (0.6)	>.99
≤30 d	3/667 (0.4)	0/330 (0)	.55
>30 d	2/646 (0.3)	2/317 (0.6)	.60
ARC			
Definite	5/652 (0.8)	0/319 (0)	.18
Probable	2/652 (0.3)	2/319 (0.6)	.60
Possible	4/652 (0.6)	2/319 (0.6)	>.99
Definite or probable	7/652 (1.1)	2/319 (0.6)	.73
Any	11/652 (1.7)	4/319 (1.3)	.78
Target lesion revascularization	22/655 (3.4)	18/321 (5.6)	.12
Target vessel revascularization	40/655 (6.1)	24/321 (7.5)	.41
Target vessel revascularization remote	20/655 (3.1)	14/321 (4.4)	.35
Major adverse cardiac events[a]	39/653 (6.0)	33/320 (10.3)	.02
Target vessel failure[a]	56/653 (8.6)	36/320 (11.3)	.20

Abbreviations: ARC, Academic Research Consortium.[14]

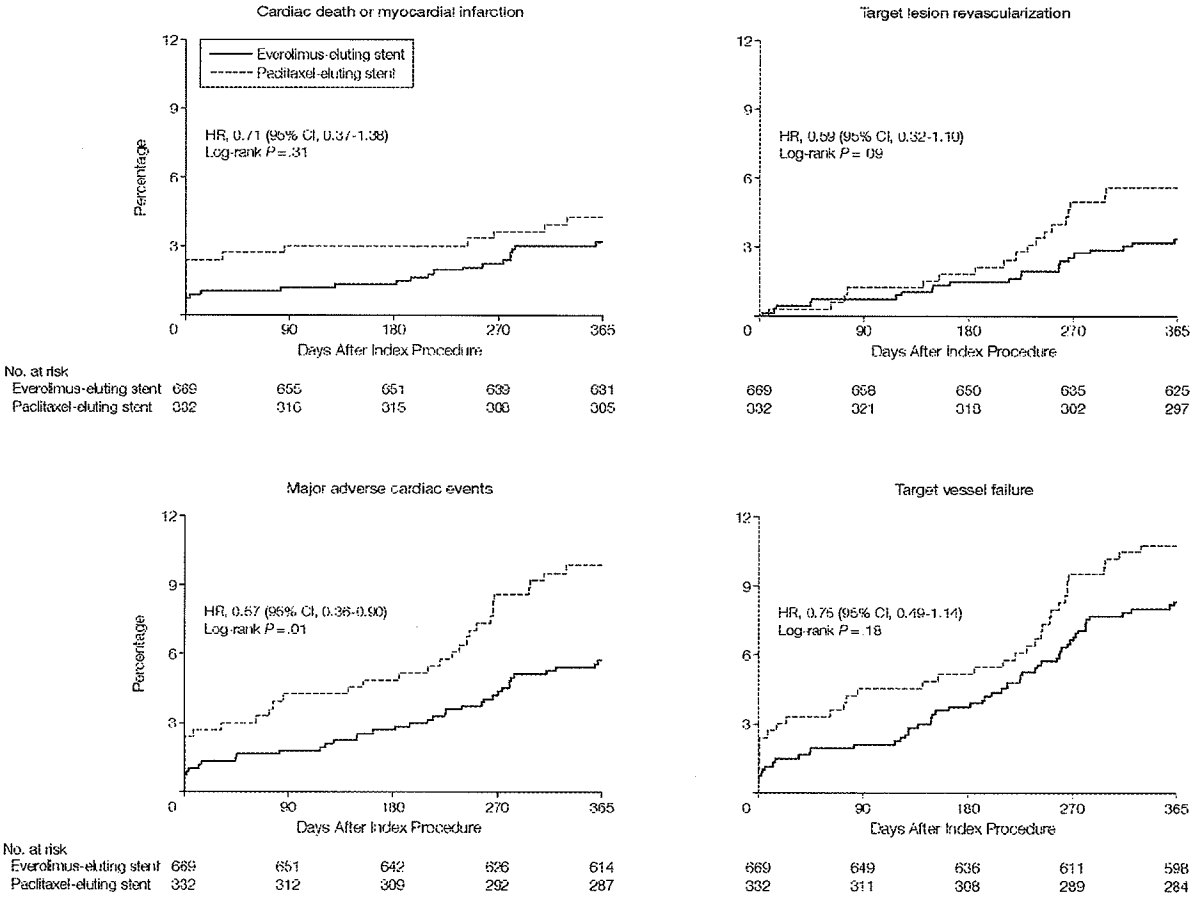
[a] Per the statistical analysis plan, since the composite target vessel failure and major adverse cardiac event end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator.

of patients receiving everolimus stents and paclitaxel stents, respectively (P=.15), and a thienopyridine (clopidogrel or ticlopidine) was being taken by 71.2% and 70.4%, respectively (P=.82).

Subgroup Analysis

A post hoc linear regression analysis with formal interaction testing was performed to explore whether the reduction of the primary end point of in-segment late loss at 8 months with the everolimus stent compared with the paclitaxel stent was consistent across important subgroups (of which diabetes and the number of treated vessels were prespecified). As shown in FIGURE 3, there were no significant interactions between treatment assignment and angiographic outcomes among 7 subgroups, with the exception of age. Logistic regression analysis with interaction testing was also performed to explore whether the reduction in major adverse cardiac events with the everolimus stent compared with the paclitaxel stent present at 1 year was consistent across important subgroups. As shown in FIGURE 4, there were no significant interactions between treatment assignment and outcomes at 1 year among 8 subgroups, with the exception of patients with diabetes. The relative reduction in major adverse cardiac events with everolimus stents compared with paclitaxel stents was comparable in patients both undergoing and not undergoing 8-month follow-up angiography. Among patients in the angiographic follow-up cohort, target lesion revascularization in the everolimus and paclitaxel stent groups was required in 15 of 368 (4.1%) vs 12 of 181 (6.6%) patients, respectively (relative

Figure 2. Time-to-Event Curves for Cardiac Death or Myocardial Infarction, Target Lesion Revascularization, Major Adverse Cardiac Events, and Target Vessel Failure Among Patients Randomized to Receive the Everolimus-Eluting Stent and the Paclitaxel-Eluting Stent



Event rates presented here were calculated by Kaplan-Meier methods and compared with the log-rank test and differ slightly from those in the text and Table 3, which were calculated as categorical variables and compared with the Fisher exact test. In each panel, initial number at risk for the paclitaxel stent differs from the number randomized because 1 patient did not sign informed consent. CI indicates confidence interval; HR, hazard ratio.

risk, 0.61 [95% CI, 0.29 to 1.29]; $P=.21$), whereas in the nonangiographic follow-up cohort the target lesion revascularization rates were 7 of 285 (2.5%) vs 6 of 139 (4.3%), respectively (relative risk, 0.57 [95% CI, 0.19 to 1.66]; $P=.37$).

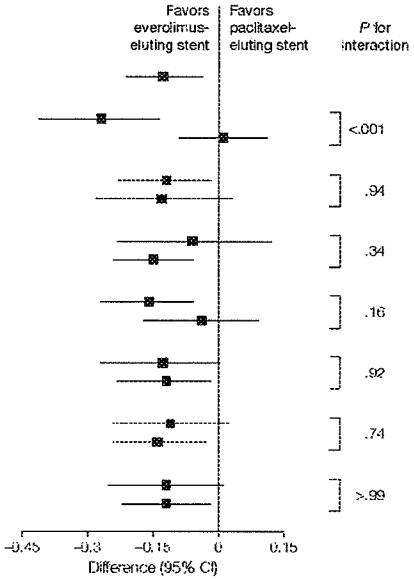
COMMENT

This large-scale, prospective, randomized, single-blind, controlled study demonstrates that an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent results in a significant reduction in angiographic in-segment late loss at 8 months, with noninferior 9-month rates of ischemia-driven target vessel failure. Thus, the 2 prespecified FDA regulatory requirements required for the trial to be considered successful were met. The reduction in late loss was confirmed by the findings from intravascular ultrasound, which demonstrated an approximate 50% reduction in volumetric neointimal hyperplasia. As a result, even though the trial was not powered for a reduction in binary angiographic restenosis, a strong trend was present in this direction favoring the everolimus-eluting stent.

Notably, the everolimus stent compared with the paclitaxel stent resulted in a significant 42% reduction in major adverse cardiac events at 1 year. As such, the present study is the first pivotal randomized trial to demonstrate enhanced event-free survival with a new stent compared with any of the 3 drug-eluting stents commercially available in the United States for on-label lesions (ie, those for which treatment with drug-eluting stents has been approved by the FDA). As defined in this trial, major adverse cardiac events is a composite measure of safety (cardiac death and myocardial infarction) and stent efficacy (target lesion revascularization), which is more specific to the action of the stent than is target vessel failure (which includes the occurrence of target vessel revascularization remote from the target lesion, which would not be expected to be affected by stent implantation). The reduction in composite major adverse cardiac events with the everolimus stent was attributable to fewer postprocedural non–Q-wave myocardial infarctions and late target lesion revascularizations due to the reduction in restenosis. In this regard the results of SPIRIT III confirm and extend those from the smaller (300 patients) randomized SPIRIT II trial, in which the 1-year rates of major adverse cardiac events (using the same definition) were decreased from 9.2% with a paclitaxel-eluting stent to 2.7% with an everolimus-eluting stent ($P=.04$), also due to fewer cardiac deaths, myocardial infarctions, and target lesion revascularizations.[19] Reduction in procedural-related myonecrosis with the everolimus stent may result from less side-branch compromise due to the thinner polymer (7.8 μm vs 16.0 μm) and total polymer plus stent strut width (89 vs 148 μm) compared with the paclitaxel stent,[20] though detailed angio-

Figure 3. Subgroup Analyses of the Primary End Point of 8-Month Angiographic In-Segment Late Loss Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent

	No. of randomized lesions		In-segment luminal late loss, mean (SD), mm					
	Everolimus-eluting stent	Paclitaxel-eluting stent	Everolimus-eluting stent	Paclitaxel-eluting stent	Difference (95% CI)	Favors everolimus-eluting stent	Favors paclitaxel-eluting stent	*P* for interaction
Angiographic follow-up cohort	343	158	0.14 (0.39)	0.26 (0.46)	−0.13 (−0.21 to 0.04)			
Age								
≥Median (63 y)	171	76	0.12 (0.37)	0.39 (0.55)	−0.27 (−0.41 to 0.14)			<.001
<Median	172	82	0.16 (0.42)	0.15 (0.33)	0.01 (−0.09 to 0.11)			
Sex								
Men	250	108	0.13 (0.34)	0.25 (0.49)	−0.12 (−0.23 to −0.02)			.94
Women	93	50	0.16 (0.51)	0.29 (0.41)	−0.13 (−0.28 to 0.03)			
Diabetes								
Yes	96	31	0.18 (0.54)	0.24 (0.40)	−0.06 (−0.23 to 0.12)			.34
No	247	127	0.12 (0.34)	0.27 (0.48)	−0.15 (−0.24 to −0.06)			
No. of treated vessels								
Single	258	110	0.13 (0.41)	0.30 (0.49)	−0.16 (−0.27 to −0.06)			.16
Dual	85	48	0.14 (0.33)	0.18 (0.39)	−0.04 (−0.17 to 0.09)			
Target vessel								
LAD	135	68	0.13 (0.40)	0.26 (0.49)	−0.13 (−0.27 to 0.00)			.92
Non-LAD	208	90	0.14 (0.39)	0.26 (0.45)	−0.12 (−0.23 to −0.02)			
RVD								
>Median (2.775 mm)	166	88	0.18 (0.38)	0.29 (0.54)	−0.11 (−0.24 to 0.02)			.74
≤Median	177	70	0.10 (0.41)	0.24 (0.36)	−0.14 (−0.24 to −0.03)			
Lesion length								
>Median (13.7 mm)	169	82	0.19 (0.47)	0.31 (0.51)	−0.12 (−0.25 to 0.01)			>.99
<Median	174	74	0.09 (0.30)	0.21 (0.40)	−0.12 (−0.22 to −0.02)			

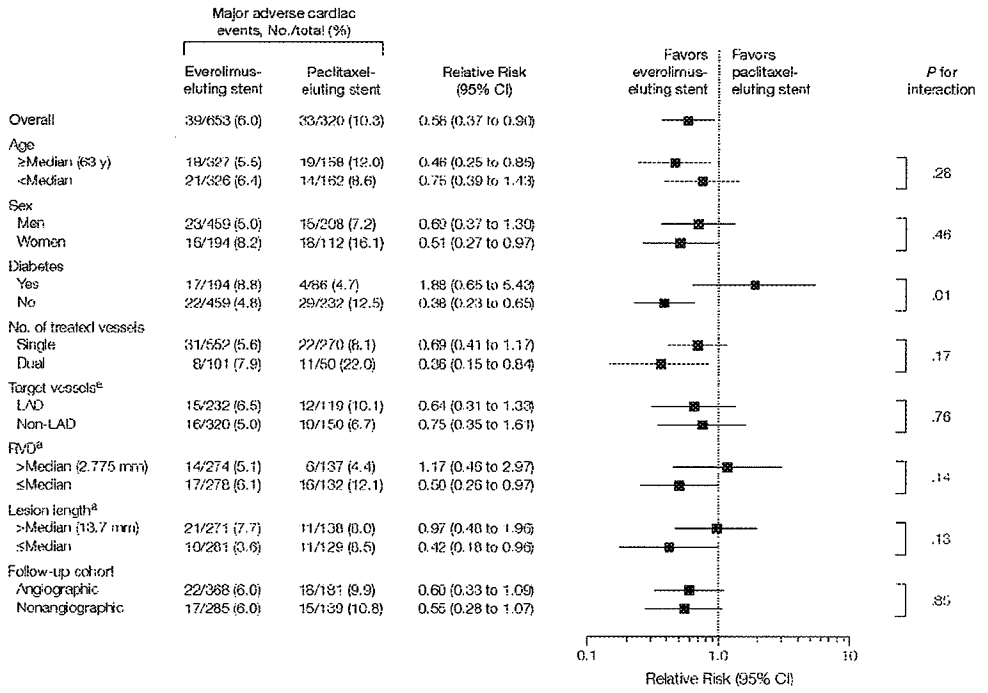


Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.

graphic study is required to confirm this possibility. Importantly, there were no significant differences in the occurrence of stent thrombosis through 1 year between these 2 devices, though this trial was underpowered to reliably evaluate this event; also, longer-term follow-up is required, because the incremental risk of stent thrombosis with drug-eluting stents may emerge beyond 1 year.[4] The lower rate of target lesion revascularization with the everolimus stent compared with the paclitaxel stent may be directly attributed to the reduction in late loss and smaller follow-up diameter stenosis in the target lesion, as recently described.[21]

The reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent was consistent across multiple important subgroups except when stratified by age. No significant differences in angiographic outcomes were present between the 2 stents in young patients, whereas assignment to receive the everolimus stent rather than the paclitaxel stent was associated with a marked reduction in late loss in elderly patients. Given the lack of an interaction with reference vessel diameter and lesion length, an explanation underlying this finding is not immediately evident. Of note, no interaction was present between diabetic status and angiographic late loss, signifying a significant reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent in patients both with and without diabetes. In contrast, a significant interaction was present between diabetes and stent type on the major adverse cardiac event end point, a finding that contributes to the conflicting reports from prior studies examining the relative safety and efficacy of paclitaxel-eluting compared with sirolimus-eluting stents in patients with diabetes.[22-25] However, this difference was driven by the 62% lower rate of major adverse cardiac events in patients with diabetes who were treated with paclitaxel stents compared with patients without diabetes who also were treated with paclitaxel stents, an unlikely finding that may have been due to chance alone. The differences between the 2 devices were also less apparent in larger vessels (which, compared with small vessels, may be able to accommodate more neointimal hyperplasia before the ischemic threshold is reached)[21] and in longer lesions (which, compared with shorter lesions, may have a greater statistical likelihood of restenosis developing in a

Figure 4. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent



Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.

[a]Analysis restricted to patients undergoing treatment of a single lesion.

single spot, despite less volumetric neointimal hyperplasia). Moreover, no differences were evident in the beneficial effect of the everolimus stent compared with the paclitaxel stent in reducing the occurrence of major adverse cardiac events as a function of age. All of these subgroup findings should be considered hypothesis-generating, because subgroup analysis is inherently underpowered and statistical adjustments were not made for multiple comparisons leading to possible false-positive findings.[26]

The strengths and limitations of the present investigation should be considered. That composite major adverse cardiac events have now been shown to be reduced with an everolimus stent compared with a paclitaxel stent in 2 consecutive randomized trials performed at different institutions in different geographies (United States vs Europe and Asia Pacific)[19] increases the likelihood that this finding is real. Despite the dilutive effect of including target vessel revascularization in the target vessel failure end point, a trend was also present toward a 24% reduction with the everolimus stent in this composite measure at 1 year. Moreover, the clinical and angiographic outcomes with the paclitaxel stent in the present study were similar or better than those observed in earlier trials with this device in comparable patients and lesions,[2] and as such underperformance of the control stent does not explain this finding. However, while SPIRIT III is the largest completed trial to date investigating an everolimus-eluting stent, major adverse cardiac events were not the primary end point of this study (nor of SPIRIT II), and therefore this conclusion cannot be considered definitive until prospectively verified in an adequately powered randomized trial. The present trial also was underpowered to examine whether an everolimus stent reduces target lesion revascularization, target vessel revascularization, and target vessel failure as well as the occurrence of low-frequency safety events, compared with a paclitaxel stent. That angiographic follow-up was performed in 43.5% of patients in the present trial further raises concern whether the greater late loss with the paclitaxel stent compared with the everolimus stent may have triggered a greater proportion of excess revascularization procedures in the former group (the "oculostenotic reflex"),[27] although such a bias was not apparent in subgroup analysis. Logistic considerations precluded blinding the operator to the stent type, although clinical follow-up assessment, core laboratory, and clinical events committee personnel were blinded to randomization group, and source-documented ischemia or a severe stenosis by quantitative analysis was required to be present for declaration of target lesion or vessel revascularization. The results of the present trial cannot be extended to patient and lesion types excluded from enrollment. Also, complete screening log data are not available, and thus the proportion of patients undergoing percutaneous coronary intervention who were eligible for enrollment in this study is unknown. Finally, the current study was not designed to elicit other potential advantages of the everolimus stent, such as its greater flexibility and deliverability in complex coronary anatomy.

In summary, in this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent in de novo native coronary artery lesions resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

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